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REVIEW

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The Status of Carbapenem Resistance in Cystic Fibrosis: A Systematic Review and Meta-Analysis

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Background: Antibiotic resistance in cystic fibrosis (CF) is a well-known phenomenon. However, the comprehensive epidemiological impact of antibiotic resistance in CF is not clearly documented. So, this meta-analysis evaluated the proportion rates of carbapenem resistance (imipenem, meropenem, and doripenem) in CF based on publication date (1979-2000, 2001-2010, and 2011-2021), continents, pathogens, and antimicrobial susceptibility testing (AST). **Methods**: We searched studies in PubMed, Scopus, and Web of Science (until April 2021). Statistical analyses were conducted using STATA software (version 14.0). **Results**: The 110 studies included in the analysis were performed in 25 countries and investigated 13,324 pathogens associated with CF. The overall proportion of imipenem, meropenem, and doripenem resistance in CF were 43% (95% CI 36-49), 48% (95% CI 40-57), 28% (95% CI 23-33), and 45% (95% CI 32-59), respectively. Our meta-analysis showed that trends of imipenem, meropenem, and doripenem-resistance had gradual decreases over time (1979-2021). This could be due to the limited clinical effectiveness of these antibiotics to treat CF cases over time. Among the opportunistic pathogens associated with CF, the highest carbapenem resistance rates were shown in *Stenotrophomonas maltophilia*, *Burkholderia* spp., *Pseudomonas aeruginosa*, and *Staphylococcus aureus*. The highest and lowest carbapenem resistance rates among *P. aeruginosa* in CF patients were shown against meropenem (23%) and doripenem (39%). **Conclusions**: We showed that trends of carbapenem resistance had decreased over time (1979-2021). This could be due to the limited clinical effectiveness of these antibiotics to treat CF cases over time. Plans should be directed to fight biofilm-associated infections and prevent the emergence of mutational resistance. Systematic surveillance for carbapenemase-producing pathogens in CF by molecular surveillance is necessitated.

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Abbreviations: CF, cystic fibrosis; WPR, Weighted pooled resistance; AST, Antimicrobial susceptibility testing; AMR, Antimicrobial resistance; CI, Confidence interval.

Keywords: cystic fibrosis, antimicrobial resistance, carbapenem resistance, bacterial pathogens, systematic review and meta-analysis

INTRODUCTION

The autosomal recessive monogenetic disorder cystic fibrosis (CF) was once untreatable and deadly in childhood among those ethnically White/of European ancestry, occurring in ~1 in 3,400 live births; while in other ethnic groups, the rates are much lower [1-3]. Chronic suppurative airway infection is a hallmark feature of CF led by the opportunistic pathogens and their long-term persistence [4]. Human bacterial pathogens such as *Pseudomonas aeruginosa*, *Staphylococcus aureus*, *Burkholderia*, and *Stenotrophomonas* are the key contributors to morbidity and mortality in CF patients [4,5]. Carbapenems are a potent, broad-spectrum class of antibiotics that act as bactericidal inhibitors of the bacterial cell wall [6]. Carbapenems include imipenem and meropenem for the treatment of *P. aeruginosa* or *S. aureus* infections in people suffering CF [7]. However, antimicrobial resistance in CF is well-recognized phenomenon [8]. But, the global epidemiological impact of antimicrobial resistance in CF is not clearly understood. To answer this vexing question, the main objective of this review was to provide extensive data on the carbapenem resistance in CF.

METHODS

This review is reported in accordant with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines (PRISMA) [9].

Search Strategy and Study Selection

We systematically searched for relevant articles in PubMed, Scopus, and Web of Science (until April 22, 2021) by using the related keywords: ("cystic fibrosis") AND ("antibiotic resistance" OR "drug resistance" OR "antimicrobial resistance" OR "carbapenems resistance") in the Title/Abstract/Keywords fields. No limitation was conducted while searching databases. The search strategy was designed and conducted by study investigators. Authors cross-checked included articles reference lists for any additional studies that may have been missed in the search. The records found through database searching were merged and the duplicates were removed using EndNote X8 (Thomson Reuters, New York, NY, USA). One of the team researchers randomly evaluated the search results and confirmed that no relevant study had been ignored. All these steps were done by three authors and any disagreements about article selection were resolved through discussion, and a fourth author acted as arbiter. Three reviewers screened all titles and abstracts separately and excluded irrelevant or duplicate articles first. Afterward, they evaluated the remaining articles for inclusion separately. Discrepancies were resolved by discussion.

Data Extraction

The following items were extracted from included studies: first author, year of study, year published, continent, country, number of pathogens (*P. aeruginosa*, *S. aureus*, *S. maltophilia*, *Burkholderia* species, nontuberculous *Mycobacteria* (NTM), and other bacterial species), number of carbapenem-resistant pathogens, and antimicrobial susceptibility testing (AST; automated system, disk diffusion, dilution methods, and MIX). The exclusion criteria were as follows: (1) studies that contained duplicate data or were overlapping articles; (2) animal research, reviews, meta-analysis and/or systematic review, and conference abstracts; and (3) carbapenem-resistance rates were not presented or reported.

Quality Assessment

The quality of the included studies was assessed using an adapted version of the tool proposed by the Newcastle-Ottawa assessment scale adapted for cross-sectional studies [10]. A score ranging from 0 to 7 points was attributed to each study (≥ 6 points: high quality, ≤ 5 points: low quality).

Statistical Analysis

The included studies presenting raw data on carbapenem resistance in CF was performed by computing the pooled using a random-effects model with Stata/SE software, v.14.1 (StataCorp. 2015. Stata Statistical Software: Release 14. College Station, TX: StataCorp LP.). Weighted pooled resistance rate (WPR: proportion of strains resistant to specific antimicrobial agents) was calculated based on the Freeman-Tukey double-arcsine transformation. The inconsistency across studies was examined by the forest plot as well as the I^2 statistic. Values of I^2 (25%, 50%, and 75%) were interpreted as the presence of low, medium, or high heterogeneity, respectively. So, the DerSimonian and Laird random effects models were used [11]. Publication bias was analyzed using Egger's linear regression test. All statistical interpretations were reported on a 95% confidence interval (CI) basis.

Study Outcomes

The main outcome of interest was the WPR rates of carbapenem resistance (imipenem, meropenem, and doripenem) in CF. A subgroup analysis was performed by; (1) publication date (1979-2000, 2001-2010, and 2011-2021), (2) geographic areas (continents), (3) pathogens, (4) AST.

RESULTS

Systematic Literature Search

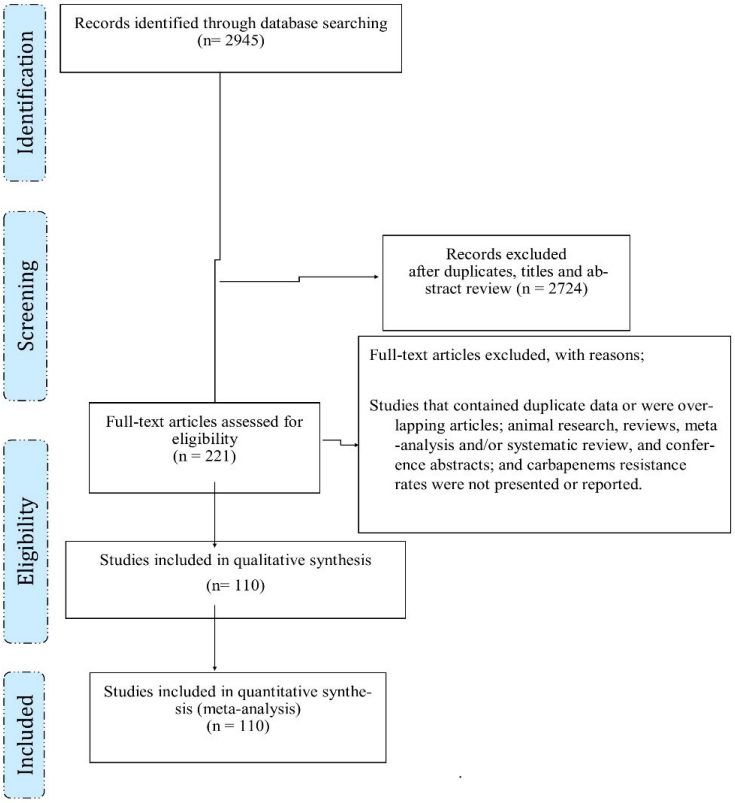

Figure 1. **Flow chart of study selection**.

A total of 2,945 records were identified in the initial search. Among these, 2,724 articles were excluded after an initial screening of the title and abstract due to their irrelevance and duplication. The full texts of the remaining 200 articles were reviewed (Figure 1). Of 221 articles, 111 were excluded for the reasons as above mentioned. Finally, 110 studies [12-121] were included in this meta-analysis. The studies included in this meta-analysis evaluated antibiotic resistance to imipenem, meropenem, and doripenem. The final studies included in the analysis were performed in 25 countries and investigated 13,324 pathogens associated with CF. The WPR rates for each antimicrobial are shown in Table 1 and Figure 2.

META-ANALYSIS

Carbapenem Resistance

Imipenem: Susceptibility to imipenem was determined in 14,459 bacterial pathogens associated with CF; the WPR was 43% (95% CI 36-49) with substantial heterogeneity (I^2=98.27%) (Table 1 and Figure 2). To analyze the trends for changes in the prevalence of imipenem-resistance in CF in more recent years, we performed a subgroup analysis for three periods 1979-2000, 2001-2010, and 2011-2021) (Table 1, Figure 3). The subgroup analysis that compared the data from 1979-2000 (WPR 60%; 95% CI 38-59), 2001-2010 (WPR 46%; 95% CI 33-59), and 2011-2021 (WPR 38%; 95% CI 31-46) indicated a significant decrease in the resistance rate (P <0.001) (Table 1, Figure 3). The highest imipenem resistance rate was shown in Europe, followed by North America (50%, 95% CI 42-57; 48%, 95% CI 25-72). Among 23 countries reporting resistance data for imipenem, 12 (52.1%) countries (China, Iraq, Scotland, Denmark, London, Turkey, Ireland, Italy, Germany, Argentina, US, and UK) reported that > 43% of isolates had imipenem resistance. The highest imipenem resistance rate was shown in *S. maltophilia*, non-tuberculous *mycobacteria*, and *Burkholderia* spp., followed by (99%, 95% CI 96-100; 75%, 95% CI 46-96; and 55%, 95% CI 42-68) (Table 1). Statistically, a significant difference was found in the subgroups AST, continents, and pathogens (P <0.001).

Meropenem: Susceptibility to meropenem was determined in 17,032 bacterial pathogens associated with CF; the WPR was 28% (95% CI 23-33) with substantial heterogeneity (I^2=97.55%) (Table 1). As shown in the Table 1 and Figure 3, the prevalence of meropenem resis-

Table 1. Prevalence of Carbapenem Resistance in Cystic Fibrosis Based on Years, Pathogens, AST, and Continents

Variables	Proportion (%) (95% CI)	n, N	Heterogeneity (I^2) (%)	Egger test
Imipenem				
Overall	43 (36, 49)	6389, 14459	98.27	0.86
1979-2000	60 (38, 59)	424, 1707	97.92	
2001-2010	46 (33, 59)	3203, 6215	98.90	
2011-2021	38 (31, 46)	2762, 6537	96.89	
Nontuberculous *mycobacteria*	75 (46, 96)	177, 385	95.95	
Burkholderia spp.	55 (42, 68)	898, 1219	94.52	
P. aeruginosa	34 (28, 40)	3817, 9848	97.51	
S. maltophilia	99 (96, 100)	1161, 1189	78.14	
Others	20 (10, 32)	336, 1818	96.03	
Asia	22 (2, 49)	217, 531	97.92	
Europe	50 (42, 57)	4456, 10887	98.00	
North America	48 (25, 72)	1372, 2165	99.15	
South America	10 (3, 21)	103, 432	91.35	
Oceania	30 (4, 66)	111, 273	98.11	
Africa	8 (1, 26)	2, 25	-	
Automated system	12 (5, 20)	23, 188	-	
Disk diffusion	43 (32, 54)	1081, 2490	97.04	
Dilution methods	50 (40, 60)	4972, 10909	98.91	
MIX	26 (15, 38)	313, 872	92.04	
Meropenem				
Overall	28 (23, 33)	6410, 17032	97.55	0.17
1979-2000	7 (6, 9)	78, 1051	-	
2001-2010	27 (20, 36)	3282, 7936	97.77	
2011-2021	29 (23, 35)	3050, 8045	96.69	
Nontuberculous *mycobacteria*	-	-	-	
Burkholderia spp.	38 (28, 47)	1552, 3219	88.28	
Streptococcus spp.	7 (1, 15)	7, 73	-	
P. aeruginosa	23 (18, 28)	4101, 12478	97.59	
S. aureus	53 (28, 77)	9, 17	-	
S. maltophilia	97 (92, 100)	471, 487	66.76	
Others	18 (7, 33)	270, 758	93.66	
Asia	14 (0, 51)	154, 324	97.01	
Europe	35 (28, 41)	4504, 12268	97.65	
North America	41 (29, 53)	1520, 3453	96.13	
South America	14 (1, 34)	65, 272	94.41	
Oceania	3 (0, 9)	59, 274	92.19	
Africa	8 (1, 26)	2, 25	-	
Automated system	6 (2, 14)	5, 75	-	
Disk diffusion	25 (17, 34)	1399, 3563	97.03	

Dilution methods	31 (24, 38)	4721, 12585	98.12	
MIX	27 (15, 40)	285, 809	92.74	
Doripenem				
Overall	45 (32, 59)	374, 795	90.76	0.91
1979-2000	-	-	-	
2001-2010	49 (45, 53)	294, 600	-	
2011-2021	42 (13, 74)	80, 195	93.65	
Non-tuberculous *mycobacteria*	-	-	-	
Burkholderia spp.	51 (31, 80)	120, 231	74.07	
Streptococcus spp.	-	-	-	
S. maltophilia	-	-	-	
P. aeruginosa	39 (22, 58)	254, 564	94.42	
S. aureus	-	-	-	
Others	-	-	-	
Asia	0 (0, 6)	2, 52		
Europe	63 (40, 84)	78, 143	83.69	
North America	49 (45, 53)	294, 600	-	
South America	-	-	-	
Oceania	-	-	-	
Africa	-	-	-	
Automated system	-	-	-	
Disk diffusion	75 (57, 90)	23, 31	-	
Dilution methods	49 (43, 56)	349, 712	66.52	
MIX	0 (0, 6)	2, 52	-	

tance notably increased from 7% (95% CI 6-9) of 1,051 strains in 1979-2000 reaching 27% (95% CI 20-36) of 7,936 strains in 2001-2010. The frequency of meropenem resistance during the years 2011-2021 represents a gradual increase from the years 2001-2010. However, there was significant variation in the proportion of meropenem resistance isolates over time (P <0.01). The highest meropenem resistance rate was shown in North America, followed by Europe (41%, 95% CI 29-33; 35%, 95% CI 28-41). Among 22 countries reporting resistance data for meropenem, 10 (~45.45%) countries (China, Scotland, Portugal, Spain, Turkey, Ireland, Italy, US, UK, and France) reported that > 28% of isolates had meropenem resistance. The highest meropenem resistance rate was shown in *S. maltophilia* followed by *S. aureus* (97%, 95% CI 93-100; 53%, 95% CI 28-77) (Table 1). Statistically, a significant difference was found in the subgroups AST, continents, and pathogens (P <0.001).

Doripenem: Susceptibility to doripenem was determined in 795 bacterial pathogens associated with CF; the WPR was 45% (95% CI 32-59) with substantial heterogeneity (I^2=90.76%) (Table 1). The subgroup analysis that compared the data from 2001-2010 (WPR 49%; 95% CI 45-53) and 2011-2021 (WPR 42%; 95% CI 13-74) indicated a minor decrease in the resistance rate (P <0.001) (Table 1, Figure 3). The highest doripenem resistance rate was shown in Europe, followed by North America (63%, 95% CI 40-84; 49%, 95% CI 45-53). Among 27 countries reporting resistance data for doripenem, five countries (including the US, Argentina, and Denmark) reported that >45% of isolates had resistance. The highest doripenem resistance rate was shown in *Burkholderia* spp., followed by *P. aeruginosa* (51%, 95% CI 31-80; 39%, 95% CI 22-58) (Table 1). Statistically, a significant difference was found in the subgroups AST, continents, and pathogens (P <0.001).

PUBLICATION BIAS

Egger's regression tests were performed to assess small study effect, and the results for each antibiotic were mentioned in Table 1. Egger's regression tests were conducted to evaluate the influence of small studies as publication bias. However, the P-value of Egger's test do not support the existence of publication bias for all antibiotics (P >0.05).

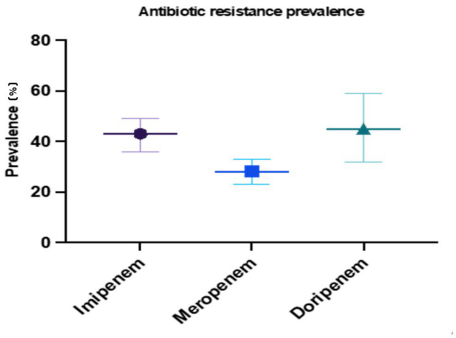

Figure 2. The prevalence of carbapenem resistance in CF.

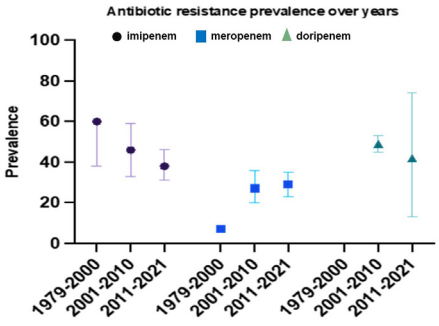

Figure 3. The prevalence of carbapenem resistance in CF stratified by publication year.

DISCUSSION

The crisis of AMR has potentially life-threatening concerns for management of infections, especially in chronic respiratory infection [5]. AMR can present major challenges in the treatment of CF lung infections [122]. This meta-analysis was conducted to consider the global status of carbapenem resistance (imipenem, meropenem, and doripenem) in CF. It is important to obtain further data about the carbapenem resistance profiles of circulating bacterial pathogens associated with CF. *P. aeruginosa*, *S. aureus*, *S. maltophilia*, and *Burkholderia* spp. remain the most frequent pathogens associated with CF patients [123].

Carbapenems such as imipenem, meropenem, and doripenem are potent broad-spectrum antimicrobial agents commonly used for treating of bacterial infections with these bacteria [6,124,125]. However, the increasing emergence and rapid development of resistance to these antibiotics, mainly among Gram-negative pathogens, dramatically limits treatment options in many countries and constitutes a major threat to global health [6,124,125]. Persistent colonization and infections with drug resistant pathogens have been associated with the progression of lung damage and raised morbidity and mortality among CF patients [126].

In 110 included studies, the prevalence of imipenem, meropenem, and doripenem resistance in CF was 43%, 28%, and 45%, respectively. Our meta-analysis showed that except meropenem, trends of imipenem and doripenem-resistance had decreased over time (1979-2021). This could be due to the limited clinical effectiveness of these antibiotics to treat CF cases over time. Regarding meropenem resistance, a huge increase was noted from the earlier time period of 1979-2000 to the period 2001-2010, but this was based on a single study [127]. Due to more frequent severe recessive disorder in people of European descent, strong clinical awareness, and greater health facilities, it should be stated that most of reports were from Europe and North America countries [128]. Thus, our meta-analysis displays that the data are biased towards Europe and North America and the frequency of carbapenem-resistance of CF in Europe and North America were much higher than comparing with other continents. In Asian and African countries, the national CF registration system is mostly lacking, or it is individualized-based research due to civil war, poverty, malnutrition, and outbreaks of infectious diseases. The WHO has already listed CF as a significant disorder and requested all countries to update their data and reports on CF cases that underlines the urgent need for revitalization of national and global CF registration, worldwide [129]. Among the opportunistic pathogens associated with CF, the highest carbapenem-resistance rates were shown in *S. maltophilia*, *Burkholderia* spp., *P. aeruginosa*, and *S. aureus*. This could be due to their biofilm formation, their long-term persistence despite rigorous antibiotic therapy, high frequency of hypermutable or mutator microorganisms in CF chronic respiratory infection [5,8,122,130,131].

P. aeruginosa is the leading cause of morbidity and mortality in CF patients [132]. The highest and lowest carbapenem-resistance rates among *P. aeruginosa* in CF patients were shown against meropenem (23%) and doripenem (39%). Several mechanisms involved in carbapenems reduced susceptibility or resistance in *P. aeruginosa* isolates including target site mutations, carbapenem-hydrolyzing enzymes (mainly metallo-β-lactamases, AmpC chromosome-encoded cephalosporinase), altered permeability via deficiency in outer membrane porin oprD (through *parRS*, *mexS*, and *czcS* genes), overproduction of active efflux systems (overexpression of the MexAB-OprM, MexCD-OprJ, and MexXY-OprM), and environmental triggers [133-136].

CONCLUSION

We indicated that trends of imipenem, meropenem, and doripenem-resistance decreased over time (1979-2021). This could be due to the limited clinical effectiveness of these antibiotics to treat CF cases over time. The relatively high carbapenem-resistant rates were shown among the opportunistic pathogens associated with CF. With changing epidemiology and antimicrobial susceptibility trending among the opportunistic pathogens associated with CF, our meta-analysis underlines the importance of continuous monitoring, which could be applied by policymakers and health workers for good management of biofilm-associated infections. Plans should be directed to fight biofilm-associated infections and prevent the emergence of mutational resistance. Systematic surveillance for carbapenemase-producing pathogens in CF by molecular surveillance is necessitated.

Availability of data and materials: All the data in this review are included in the manuscript.

Competing interests: The authors declare that they have no competing interests.

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