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A Review: Effectiveness of Cephalosporins/Siderophore Cephalosporins versus Meropenem as Therapy in Patients with Hospital Acquired Pneumonia

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Abstract

Background: Hospital-Acquired Pneumonia (HAP) is a nosocomial infection that causes mortality and morbidity. It also leads to increased length of hospitalization and cost of care. Increasing antibiotic resistance necessitates the search for alternative antibiotics, such as HAP thelimitrapy. Carbapenem antibiotics as standard HAP antibiotics and cephalosporins/cephalosporin siderophores have proven effective for infections caused by gram-negative bacteria that cause HAP. This review aimed to evaluate the combination of cephalosporins and beta-lactamase inhibitors as an effective therapy for HAP that can reduce the risk of antibiotic resistance.

Methods: Cochrane and PubMed were the sources for searching articles in this study. The articles were then selected by using the PICO method (Population, Intervention, Comparison, and Outcomes). The target population was adult HAP patients, with interventions of cefiderocol, ceftazidime-avibactam, and ceftolozane-tazobactam. The comparator in this study was meropenem, and the outcome was clinical improvement with microbiological response and mortality as the parameters. The PRISMA flow chart later described a summation of this review study.

Results: Eight articles comprehensively discussed the effectiveness of cephalosporins/siderophore cephalosporins and meropenem against *Klebsiella pneumonia, Pseudomonas aeruginosa,* and *Escherichia coli*. The clinical recovery of patients after administering these two antibiotics showed high therapeutic effectiveness and could reduce mortality. Ceftazidime-avibactam, ceftolozane-tazobactam, and cefiderocol are new antibiotics that are effective for HAP. Meropenem at high doses can offset the efficacy of the three antibiotic combinations and minimize antibiotic resistance.

Conclusion: Meropenem and cephalosporins/siderophore cephalosporins have similar effectiveness as therapy for gram-negative infections in HAP, with attention to dosage to obtain effective therapy.

Keywords: *Cephalosporins, Hospital Acquired Pneumonia, Meropenem, Nosocomial Pneumonia.*

Introduction

Hospital-Acquired Pneumonia (HAP) is a nosocomial pneumonia infection that occurs at least 48 hours or two days after hospitalization without any incubation of the disease before hospitalization[1]. HAP is the second most common hospital-acquired infection after urinary tract infections. The highest incidence of HAP occurs in immunocompromised patients, patients who have undergone surgery or post-surgery, and geriatric patients[2]. HAP causes an increase in the number of patient deaths, prolongation of patient hospitalization time, and an increase in the cost of care[3].

Timely administration of empirical antibiotics is an issue that affects the success of therapy in HAP. Timely administration of appropriate therapy can reduce mortality by about 30%. In critical patients, there are difficulties in quickly identifying the specific pathogen causing HAP. Based on Infection Diseases Society of America (IDSA) guidelines, the empirical therapy of choice in patients with HAP is meropenem. However, clinical guidelines do not always take into account individual variations among patients[4]. Carbapenems are currently the most effective beta-lactams against bacterial infections, so they are used as antibiotics of last resort but are less susceptible to most of the determinants of resistance, and the emergence and spread of resistance occurs across continents. The amount of resistance that arises causes problems in selecting empirical antibiotic therapy, so several prospective studies were conducted in various countries to obtain empirical antibiotics that are as potent as HAP therapy. Cephalosporins antibiotics have a beta-lactam ring structure that has broad activity and are used to treat various bacterial infections. When combined with beta-lactam inhibitors, they can increase the effectiveness in overcoming bacteria resistant to meropenem and, therefore, can be used as an alternative therapy for HAP.

This review article will discuss meropenem antibiotics with comparators from the cephalosporin group combined with beta-lactam groups, namely ceftazidime-avibactam, ceftolozane-tazobactam, and

cefiderocol, the three new antibiotic combinations used as an antibiotic choice in HAP and also avoid the incidence of antibiotic resistance[5,6].

Methods

This is a review of articles on meropenem antibiotics compared to cephalosporins/siderophore cephalosporins for hospital-acquired pneumonia or nosocomial pneumonia, namely Cochrane and PubMed. The search was conducted from 2013 to 2023. The search strings used were "hospital-acquired pneumonia" or "nosocomial pneumonia", "cefiderocol", "ceftazidime-avibactam", "ceftolozane-tazobactam", and "meropenem". The literature search began with identifying the Cochrane and PubMed, then screening the year published in the articles. The literature search also includes eliminating articles with limited access, duplication, and articles irrelevant to the theme from the group of articles to be discussed. From the screening results, the eligibility of each article was checked, and eight articles were obtained that met the inclusion and exclusion criteria.

This article review contains inclusion criteria: (1) Participants with a diagnosis of HAP. (2) Intervention: The experimental group received cefiderocol, ceftazidime-avibactam, and ceftolozone-tazobactam intervention therapy. (3) Comparison: Control group treated with meropenem. (4) The literature was published within the last ten years, and documents were fully accessible. (5) Main outcomes: Clinical response and mortality. The secondary outcome was a microbiological response. Exclusion criteria consisted of (1) Articles consisting only of abstracts, and conference papers. (2) Studies with incomplete data or using different control drugs. (3) Articles that were not written in English.

Data were extracted based on author name, year of publication, country where the study was conducted, number of participants, sample size, age distribution, study design, intervention, patient characteristics at the start of the study, comparators, and outcome information. The PRISMA flowchart was used as a model in the article selection process (Figure 1).

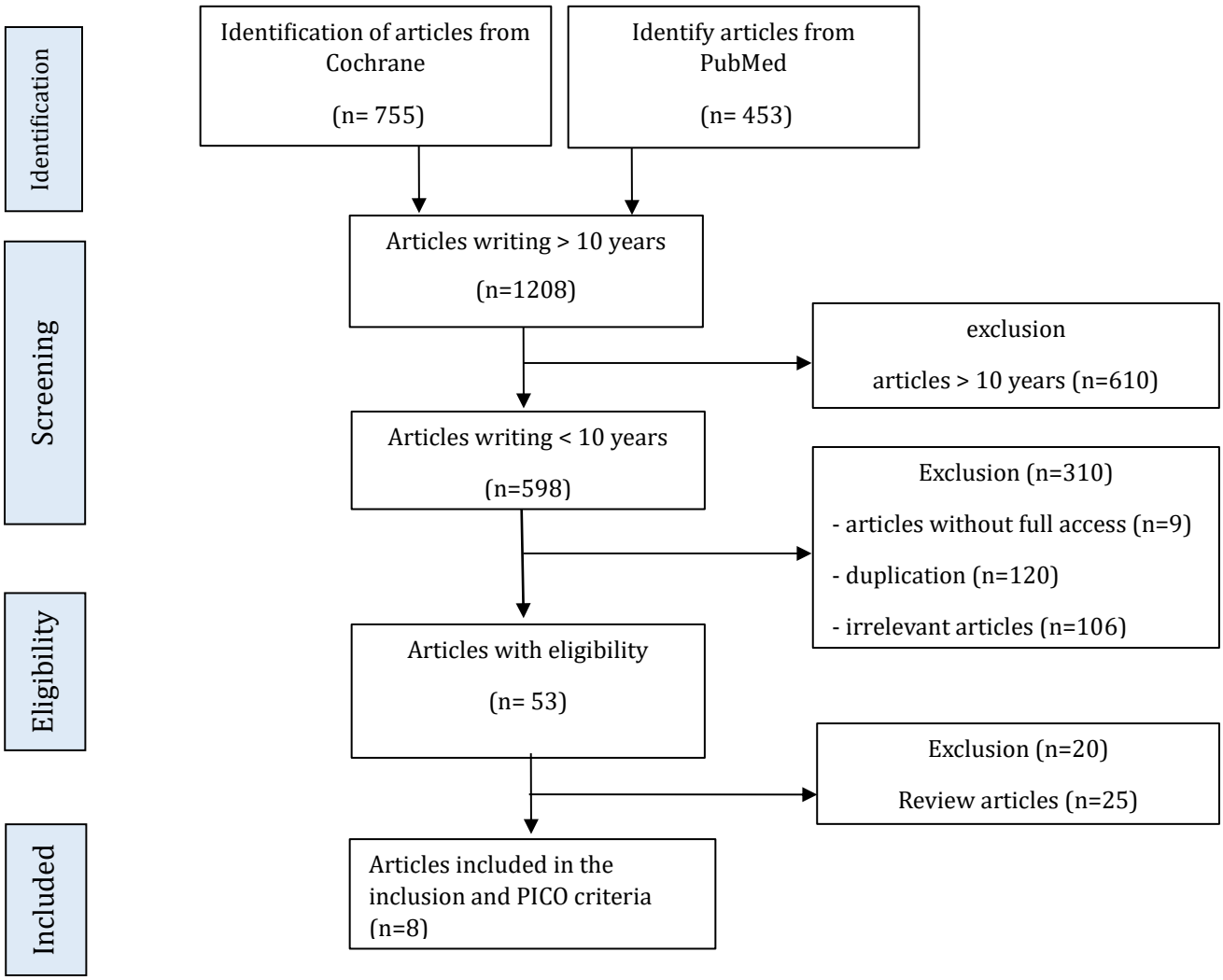

Figure 1. Search method and article selection process (PRISMA flowchart)

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Result

A search through Cochrane and PubMed identified 598 studies. After removing articles that did not evaluate antibiotic treatment for HAP or nosocomial pneumonia, 53 relevant studies remained, and only eight studies met the predefined inclusion criteria. There were three evaluation comparison groups: cefiderocol versus meropenem, ceftazidime-avibactam versus meropenem, and ceftolozane-tazobactam versus meropenem. Clinical characteristics and cure rates can be seen in Table 1 and Table 2.

The eight articles were randomized controlled trials comparing the efficacy, mortality, and microbiological response between meropenem and cefoderocol, ceftazidime-avibactam, and ceftolozane-tazobactam (Table 1). 5 of the 8 studies were double-blind, two were open-label, and one did not report the randomized procedure. Trial characteristics and results are shown in Tables 1 and 2.

Cefiderocol vs meropenem

Studies comparing cefiderocol and meropenem show that meropenem is more effective than cefiderocol. It can be seen that the clinical condition of patients who improved with meropenem therapy was 42%, while in the cefiderocol group, it was 41%. The number is not too much different. In another study conducted by Basseti et al., similar to the previous study, meropenem still had higher effectiveness than cefiderocol, with a ratio of 63% for meropenem and 60% for cefiderocol. The results of microbiological responses in both studies illustrate that meropenem and cefiderocol have strong anti-microbial properties against *Klebsiella pneumoniae* compared to cefiderocol. However, the two studies had contradictory results in the microbiological response to *Pseudomonas aeruginosa*. In the study of Wunderink et al., meropenem was stronger, with a percentage of 71%, while in the study of Basseti et al., meropenem was less effective than cefiderocol, with a percentage of 17%. In both studies with the same results, meropenem is less effective than HAP therapy caused by *Escherichia coli*, and mortality data after 14 days of observation showed meropenem has a lower mortality rate than cefiderocol.

Based on the data above, cefiderocol is a more potent anti-microbial for *Escherichia coli* than meropenem. Meropenem is more effective against *Klebsiella pneumonia* and has a lower mortality rate after 14 days than cefiderocol.

Ceftazidime avibactam vs meropenem

Research conducted by Torres in different years with different study designs, namely double-blind in the first study and open-label in the second study, gave different results. In the first study, the microbiological response results of ceftazidime-avibactam were more potent against *Klebsiella pneumonia* with a percentage of 83.8% compared to meropenem 79.6%, while in the second study, meropenem was more potent against *Klebsiella pneumonia* with a percentage of 74.7% compared to 67.7%. In both studies, meropenem was more potent against *Pseudomonas aeruginosa*, as well as in the microbiological response to *Escherichia coli*. In the first study, there was a record of the number of mortalities, while in the second study, the number of mortalities was not submitted. The clinical cure results illustrate that meropenem is still more effective than ceftazidime-avibactam, although the percentage results are not much different.

In the results of the two studies, although the percentages were not much different, meropenem was more potent as an anti-microbial on *Escherichia coli* and Pseudomonas aeruginous than ceftazidime-avibactam. Meropenem also produced more clinical improvement than ceftazidime-avibactam.

Ceftolozane-tazobactam vs meropenem

Four studies conducted to determine the clinical outcomes of HAP patients given ceftolozane-tazobactam therapy illustrate that ceftolozane-tazobacktam provides better results in clinical cure than meropenem. Research by Johnson in 2021 showed a percentage of 94.9% for the ceftolozane-tazobactam group. The results of the microbiological response in *Klebsiella pneumonia* are slightly different. The research results by Jennifer and Loeches differed from those conducted by Kollef, where Kollef's results showed that ceftolozane-tazobactam was more potent. Likewise, with anti-microbial results against *Pseudomonas aeruginosa*, there are differences between the four studies. Two studies showed that meropenem was more potent, but two other studies described ceftolozane-tazobactam as more potent. The same thing also happened in the research results on antimicrobial *Escherichia coli*. However, the mortality results of meropenem had a higher percentage than ceftolozane-tazobactam in all studies.

The differences in the study results were due to differences in non-standardized dose regimens in each study, duration of treatment, and heterogeneous adult patients in terms of characteristics, namely concomitant infections, comorbidities and immune levels, and different APACHE II scores.

Table 1. Article characteristics

Author, year	Study design, location	Number of participants	Medication therapy
Torres, 2017	Randomized, Double-blind, 23 countries	879 participants	Ceftazidime-avibactam vs meropenem
Kollef, 2019	Randomized, double-blind, 34 countries	726 participants	Ceftolozane-tazobactam vs meropenem
Torres, 2019	Randomized, open-label, Europe and USA	580 participants	Ceftazidime-Avibactam vs meropenem
Jennifer, 2020	Randomized, USA	726 participants	Ceftolozane-tazobactam vs meropenem
Wunderink, 2020	Randomized, double-blind, parallel-group, 17 countries in Asia, Europe, and the USA	292 participants	Cefiderocol vs meropenem
Bassetti, 2020	Randomized, open-label, multicentre	152 participants	Cefiderocol vs meropenem
Johnson, 2021	Randomized, double-blind, multicentre,	117 participants	Ceftolozane/tazobactam vs meropenem
Loeches, 2022	Randomized, double-blind, multicentre	511 participants	Ceftolozane-tazobactam vs meropenem

Table 2. Microbiological response, mortality, clinical cure

Author, year	Microbiological Response						Mortality		Clinical cure	
	Klebsiella pneumoniae		*Pseudomonas aeruginosa*		*Escherichia coli*					
	C/SC	Mem	C/SC	Mem	C/SC	Mem	C/SC	Mem	C/SC	Mem
Torres, 2017	31/37 (83.8%)	39/49 (79.6%)	27/42 (64.3%)	27/35 (77.1%)	8/11 (72.7%)	14/18 (77.8%)	13 (3%)	8 (2%)	29/37 (78.4%)	39/49 (79.6%)
Kollef, 2019	157/259 (60.6%)	137/240 (57.1%)	36/63 (57.1%)	39/65 (60%)	120/195 (61.5%)	105/185 (56.8%)	87/362 (24%)	92/364 (25.34%)	193/264 (73.1%)	168/247 (68%)
Torres, 2019	44/65 (67.7%)	56/75 (74.7%)	38/64 (59.4%)	37/51 (72.5%)	12/22 (54.5%)	17/23 (73.9%)	NA	NA	155/256 (60.5%)	174/267 (65.2%)
Jennifer, 2020	38/53 (71.7%)	42/58 (72.4%)	113/170 (66,5%)	97/151 (64.2%)	23/33 (69.7%)	19/26 (73.1%)	40/227 (17.6%)	45/236 (19.1%)	125/174 (71.8%)	115/158 (72.8%)
Wunderink, 2020	31/48 (65%)	29/44 (66%)	16/24 (67%)	17/24 (71%)	12/19 (63%)	13/22 (59%)	18/145 (12.4%)	17/146 (11.6%)	59/145 (41%)	61/147 (42%)
Bassetti, 2020	8/34 (24%)	4/16 (25%)	6/17 (35%)	2/12 (17%)	1/6 (17%)	0/3 (0%)	19 (42%)	4 (18%)	24 (60%)	12 (63%)
Johnson, 2021	NA	NA	56 (94.9%)	43 (74.1%)	NA	NA	NA	NA	56 (94.9%)	43 (74.1%)
Loeches, 2022	31/53 (58.5%)	34/52 (65.4%)	36/63 (57.1%)	39/65 (60%)	11/20 (55%)	5/10 (50%)	22/150 (14.7%)	44/171 (25.7%)	189/259 (73%)	163/240 (67.9%)

C: *Cephalosporin;* ***SC:*** *Siderophore cephalosporin;* ***Mem:*** *meropenem*

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Discussion

This article review focuses on clinical cure, microbiological response, and mortality. The use of interventional and standard antibiotics ranged from 14-28 days. The dosing regimen of each study was different, with different patient characteristics.

Cefiderocol vs meropenem

Cefiderocol is a novel cephalosporin siderophore with broad activity against gram-negative bacteria, including Extended Spectrum Beta-Lactamase (ESBL)-producing *Enterobacter*, *P. aeruginosa*, and *A. baumannii*. The inhibitory power of cefiderocol is also excellent, with a low MIC value that can inhibit the growth of up to 90% of the organism[7,8]. In addition, cefiderocol has a safety profile with high doses compared to the cephalosporin group[9]. Cefiderocol demonstrated effectiveness in treating multi-drug resistance gram-negative pneumonia in patients with various comorbidities such as chronic kidney disease, chronic obstructive pulmonary disease, and diabetes mellitus[10].

Using cefiderocol and meropenem antibiotics for 14 days (plus or minus 2-3 days), cefiderocol (2g administered by infusion every 8 hours) had no lower effectiveness than meropenem (2g every 8 hours extended by infusion for 3 hours)[11]. Clinical improvement results showed 65% in patients with meropenem intervention and 67% in patients with comparator cefiderocol. The microbiological response in both meropenem and cefiderocol groups was at the same percentage of 48%. The mortality rate of cefiderocol was 7% and meropenem 9%. Monitoring mortality at day 14 was the primary outcome of interest, and the secondary outcome of interest was clinical improvement and microbiological response to the antibiotics. From the analysis results of the two groups, it was found that meropenem and cefiderocol were adequate for all groups tested both in terms of patient characteristics, namely age, renal function, clinical diagnosis, ventilation status, severity of illness, APACHE II score, and pathogen. In a study conducted by Wunderink et al. (2021;2021), the tested patient population was high-risk and critically ill patients representing nosocomial pneumonia's current epidemiology and etiology. Almost half of the patients had an APACHE II score of 16, required mechanical ventilation in 60%, and 70% were in the ICU[13]. From the culture results obtained, almost 85% of patients had gram-negative pneumonia[14].

Ceftazidime-avibactam vs meropenem

Ceftazidime-avibactam combines a third-generation cephalosporin with avibactam as a beta-lactamase inhibitor, making it a broad-spectrum antibiotic that can inhibit ESBL bacteria, *Klebsiella pneumonia*, *P. aeruginosa* which are classified as severe threats to public health[15]. In a study conducted by Torres et al[16,17], the main point in monitoring is 28 days of death after administration of ceftazidime-avibactam therapy. The results of the clinical cure and microbiological response are the study's second goal.

The use of ceftazidime-avibactam (ceftazidime 2g and avibactam 0.5g given every 8 hours for 2 hours by intravenous infusion) and meropenem (1g every 8 hours by intravenous infusion for 30 minutes) showed that meropenem required a MIC greater than and equal to 4-fold to overcome *P. aeruginosa* so that it was feared that it would lead to potential resistance that emerged in the treatment[18]. In some studies, using meropenem often results in a lower mortality rate of less than 15%[19].

The effectiveness of ceftazidime-avibactam was not affected by baseline renal status, previous antibiotic use, type of infection (ventilated or unventilated), or APACHE II score category[20]. In patients with impaired renal function, there is a fluctuating decrease in the dose of ceftazidime-avibactam, so it is necessary to increase the dose by 50% to achieve maximum effectiveness in pharmacokinetic and pharmacodynamic analyses done in previous studies[21].

Ceftazidime-avibactam had no lower efficacy than meropenem concerning patient mortality caused by HAP over 28 days. The results of the ceftazidime-avibactam research study support FDA approval of it as an antibiotic therapy for HAP. Thus, ceftazidime-avibactam is the first new gram-negative antibiotic approved in the United States to indicate HAP in over 15 years.

Ceftolozane-tazobactam vs meropenem

In previous studies, trials of new antibiotics (tigecycline, doripenem, and ceftobiprole) showed that the new antibiotics were not better than existing therapy. Under-dosing of new antibiotics may contribute to therapeutic failure. Ceftolozane-tazobactam is an antibacterial combination consisting of ceftolozane (a cephalosporin) and tazobactam, a beta-lactamase inhibitor approved for complex urinary tract and intra-abdominal infections at a dose of 1.5g (ceftolozane 1g and 0.5g tazobactam) every 8 hours[22,23]. Drug concentrations in the lungs are often lower than in plasma, and the pathogens that cause nosocomial pneumonia usually have lower antibacterial susceptibility[24]. These factors lead to insufficient drug concentrations at the site of infection, so dosing regimens in nosocomial pneumonia patients must be carefully optimized[24,25].

Several studies have been conducted to determine the effectiveness of ceftolozane-tazobactam using high doses (ceftolozane 2g and tazobactam 1g) given every 8 hours. The safety of high-dose ceftolozane-tazobactam in critical and at-risk populations was found to be safe. High-dose ceftolozane-tazobactam compared with meropenem at a dose of 1g given every 8 hours gave microbiological responses that were not clinically significant, and the comparison showed that the initial susceptibility of *P. aeruginosa* to ceftolozane-tazobactam was higher than meropenem. This was also true for *Enterobacter*. Mortality was lower in patients with pathogenic *P. aeruginosa* who were given meropenem at baseline.

Meanwhile, mortality was lower in participants with *Enterobacter* pathogens and ESBL-producing *Enterobacter* who received ceftolozane-tazobactam therapy[26]. This trial showed no difference between ceftolozane-tazobactam and meropenem on the assessment until day 28. Both are mortality, clinical cure, and microbiological response[27].

Limitations

The limitations of this study were as follows: the review only discussed interventions from specific cephalosporin classes: ceftazidime, ceftolozane, and cefiderocol; and the review was only conducted on PubMed and Cochrane databases in English, limiting the scope of this review.

Conclusions

Meropenem is still an effective antibiotic for HAP. Giving high doses can avoid the occurrence of resistance. Cefiderocol, the first siderophore-cephalosporin antibiotic, has the same effectiveness as high-dose meropenem. Ceftazidime-avibactam has received FDA approval as therapy for HAP. Ceftolozane-tazobactam can be given in high doses to achieve pharmacokinetic and pharmacodynamic targets without neurotoxic side effects and seizures, as cephalosporins do when given in high doses.

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Author Contribution

Study design	:	PR, TMA
Data acquisition	:	PR, TMA
Data analysis	:	PR, TMA, DE
Manuscript writing	:	PR, TMA, DE

Competing Interests

The author has disclosed that there are no competing interests or personal relationships that could have influenced the work reported in this study.

Abbreviation

APACHE	:	Acute physiology and chronic health evaluation
ESBL	:	Extended spectrum b-lactamase
FDA	:	Food and Drug Administration
HAP	:	Hospital-acquired pneumonia
ICU	:	Intensive Care Unit
IDSA	:	Infectious Diseases Society of America
MIC	:	Minimum inhibitory concentration
PICO	:	Patients, Intervention, Comparison, Outcome

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