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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) or nosocomial pneumonia is an infection caused mainly by gram-negative bacteria. Carbapenems and cephalosporins/cephalosporin siderophores are effective for infections caused by gram-negative bacteria. Objective: To compare the effectiveness of antibiotics from the Carbapenem group (meropenem) compared to the cephalosporin/cephalosporin siderophore group in HAP infections caused by gram-negative bacteria.

Methods: Sources of article searches used Cochrane and PubMed, which were then selected by the PICO method with a population of adult HAP patients, with comparator cephalosporins/cephalosporin siderophores that have clinical improvement outcomes with parameters of microbiological response and death, the flow chart PRISMA described it.

Results: A total of 7 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 .

Keywords: Hospital Acquired Pneumonia, meropenem, cephalosporins, 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].

Antibiotics are the primary therapy for HAP. Antibiotics kill pathogenic bacteria and reach the tissues where pathogenic bacteria grow. When the clinician makes the diagnosis, it is crucial to start therapy immediately. In critical patients, there is difficulty in quickly identifying the specific pathogen causing HAP, hence the need for empirical antibiotic therapy. The IDSA guidelines have been presented to patients with HAP as practical therapy, but clinical guidelines cannot always consider individual variations between patients [4]. Appropriate timing of treatment can reduce mortality by about 30%. The amount of resistance causes problems in selecting empirical antibiotic therapy, so several prospective studies were conducted in various countries to obtain empirical antibiotics as potent as HAP therapy. This *review* article will discuss meropenem antibiotics with comparators from the cephalosporin group combined with beta-lactam groups, namely ceftazidime-avibactam, ceftolozane-tazobactam, and cephalosporin siderophores, the three new antibiotic combinations used as an antibiotic choice in HAP and also avoid the incidence of antibiotic resistance. [5,6].

Methods

A review article on meropenem antibiotic compared with cephalosporins/cephalosporin siderophores for hospital-acquired or nosocomial pneumonia, namely Cochrane. Based on the main topic of the article, terms such as "hospital-acquired pneumonia," or "nosocomial pneumonia," "cephalosporin", and "meropenem" were selected as search keywords. Inclusion criteria were patients with HAP who were given meropenem therapy, cephalosporins/cephalosporin siderophores used as empirical therapy, adult and elderly patients published within the last ten years, and documents could be accessed in full. Exclusion criteria included articles that did not address HAP or nosocomial pneumonia and used cephalosporins/cephalosporin siderophores and meropenem as definitive antibiotics. The PRISMA flowchart was used as a model in the article selection process (Figure 1).

Result and Discussion

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 seven 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 seven articles were randomized controlled trials comparing meropenem with cephalosporin/ cephalosporin hydrophore agents (Table 1). Of the seven studies, five were *double-blind*, one was *open-label,* and one did not report the *randomized* procedure. Trial characteristics and results are shown in Tables 1 and 2.

Cefiderocol is a novel cephalosporin siderophore with broad activity against gram-negative bacteria, susceptible or non-susceptible to carbapenems, 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 organisms. [7] In addition, cefiderocol has a safety profile with high doses compared to the cephalosporin group [8].

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 (2 g every 8 hours extended by infusion for 3 hours). [9]. 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 results of the analysis 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), the patient population tested were high-risk and critically ill patients representing the current epidemiology and etiology of nosocomial pneumonia. Almost half of the patients had an APACHE II score of 16, required mechanical ventilation in 60%, and 70% were in the ICU [11]. From the culture results obtained, almost 85% of patients had gram-negative pneumonia [12].

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. [13]. In a study conducted by Torres (2018), [15] the main point in monitoring is 28 days of death after administration of ceftazidime-avibactam therapy. The results of clinical cure and microbiological response are the second goal of this study.

The use of ceftazidime-avibactam (ceftazidime 2 g and avibactam 0.5 g given every 8 hours for 2 hours by intravenous infusion) and meropenem (1 g every 8 hours by intravenous infusion for 30 minutes) showed that meropenem required an 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 treatment [16]. In some studies, using meropenem often has a lower mortality rate, less than 15% (Zhuang et al., 2022) [17].

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 [18]. 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.

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.

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 1.5 g (ceftolozane 1 g and 0.5 g tazobactam) every 8 hours [19,20]. Drug concentrations in the lungs are often lower than in plasma, and the pathogens that cause nosocomial pneumonia often have lower antibacterial susceptibility (Zhang et al., 2021) [21]. These factors lead to insufficient drug concentrations at the site of infection, so dosing regimens in nosocomial pneumonia patients must be carefully optimized [22,21].

Several studies have been conducted to determine the effectiveness of ceftolozane-tazobactam using high doses (ceftolozane 2 g and tazobactam 1 g) 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 1 g 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 [23]. This trial showed no difference between ceftolozane-tazobactam and meropenem on the assessment until day 28. Both are mortality, clinical cure, and microbiological response [24].

Conclusion

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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Figures

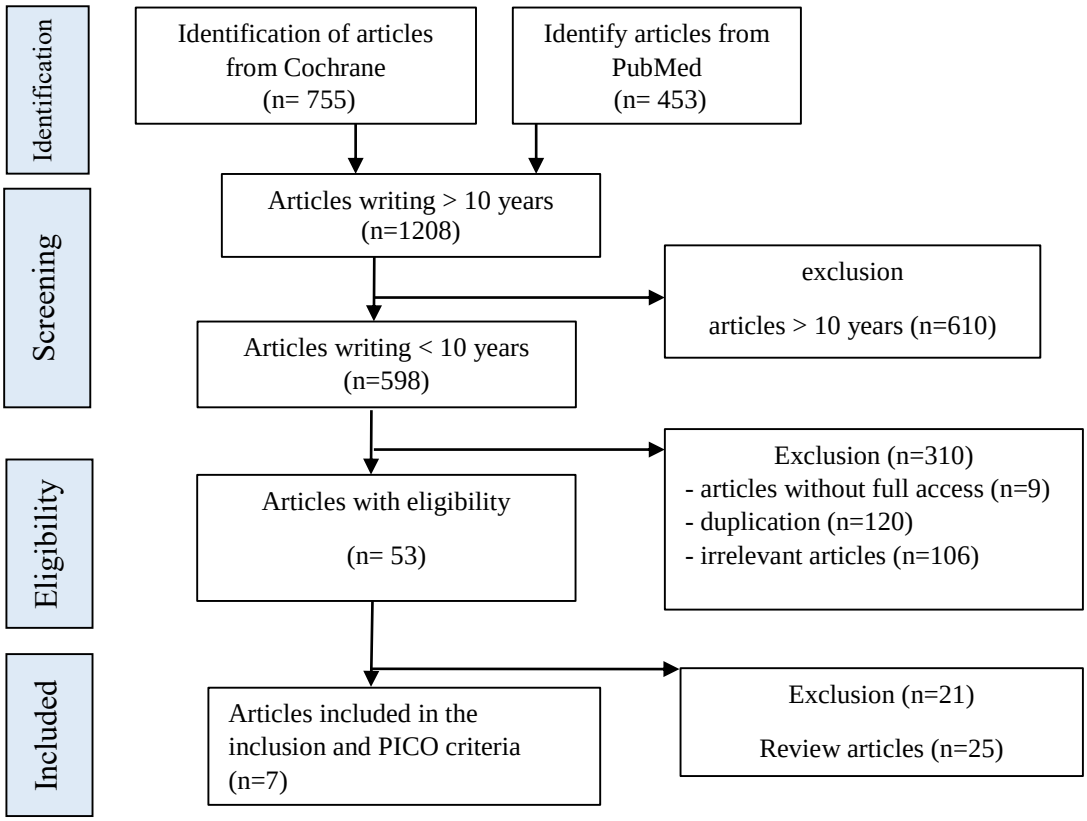

Figure 1. Search method and article selection process (PRISMA flowchart)

Tables

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
Johnson, 2021	Randomized, double-blind, multicenter,	117 participants	Ceftolozane/tazobactam vs meropenem
Loeches, 2022	Randomized, double-blind, multicenter	511 participants	Ceftolozane-tazobactam vs meropenem

Table 2: Clinical cure, mortality, microbiological response

Author, year	Clinical cure						Mortality		Microbiological Response	
	K.pneumoniae		P.aeruginosa		E.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%)
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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