

Carbapenems: A literature Review regarding Resistance, Risk Factors, and Mortality in Pneumonia

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Abstract

Carbapenem is one of antibiotic to treat respiratory infections such as pneumonia that frequently used in tertiary care facilities and started to create resistances. This study aims to review the resistance of carbapenems, assess the risk factors for resistance that leads to mortality, and the more effective antibiotic treatment options to overcome the resistance. Assessment of the use of carbapenems in pneumonia through previous studies were carried out by searching the articles in search engine databases in 2011 to 2021. Articles reporting carbapenems resistance, risk factors, and mortality were selected based on inclusion and exclusion criteria. Of 14 articles included in inclusion criteria, 4 studies reported the occurrence of resistance to gram-negative bacteria such as *Acinetobacter aumanii*, *Pseudomonas aeruginosa*, and *Klebsiella pneumoniae*, and 10 articles reported risk factors and mortality. The risk factors for carbapenems resistance are the history of carbapenems use, duration of hospitalization, use of mechanical ventilation, high Simplified Acute Physiology Score (SAPS) scores, and high Acute Physiologic and Chronic Health Evaluation (APACHE). Carbapenems resistance causes mortality such as septic shock, high Sequential Organ Failure Assessment (SOFA) scores, and elevated risk at > 60 years of age, female sex, and inappropriate choice of antibiotics. The results showed that imipenem has higher resistance than other carbapenems members, the risk factors for carbapenems resistance are dominated by a history of carbapenems use, mortality caused by high score SOFA, and colistin can be the current choice to overcome carbapenems resistance.

Keywords : Carbapenems, Pneumonia, Resistance, Risk Factor, Mortality

Introduction

Pneumonia is an infection in the lung parenchyma, precisely in the small sacs called the alveoli. This disease is caused by the invasion of microorganisms such as bacteria, viruses or fungi.^{1,2} The pathophysiology of pneumonia begins with the invasion of microorganisms that enter the alveoli in large numbers and trigger an inflammatory response from the host, access to microorganisms to reach the lower respiratory tract, and may cause septic shock and organ failure which can lead to death.³

According to the United Nations Children's Fund (UNICEF), in 2019 as many as 84% of child deaths due to pneumonia occurred in 30 countries. Children are 60 times more likely have a higher risk of death in low-income countries than in high-income countries,⁴ and the incidence in Asia reached more than 54%.^{5,6} The prevalence of under-five mortality due to pneumonia in Indonesia in 2019 was 52.9%.⁷

Antibiotics become the primary therapy for a disease that is usually caused by the bacterium *Streptococcus pneumoniae*.^{8,9} Antibiotics used as the first line of treatment for pneumonia in children and adults are penicillin, macrolides, and a combination of cephalosporins when severe pneumonia is present.^{10,11}

Antibiotic resistance in pneumonia comes from gram-positive and gram-negative bacteria such as *Streptococcus pneumoniae* (*S. pneumoniae*) which is resistant to penicillin and *Acinobacter baumannii* (*A. baumannii*) which is resistant to carbapenems.¹² Carbapenems are used as an empirical therapy for gram-negative bacteria *Klebsiella pneumoniae* (*K. pneumoniae*), *Pseudomonas aeruginosa* (*P. aeruginosa*), and MRSA (Methicillin-resistant *Staphylococcus aureus*).¹³

According to previous research on evaluating the use of carbapenems, the use of carbapenems in hospitals is increasing and resulting in resistance on gram-negative bacteria.^{14,15} Irrational use of antibiotics such as improper dosage, usage history, and excessive prescribing is a factor of resistance that can cause longer hospitalization days and mortality in patients.¹⁶⁻²⁰

This review aimed to assess the resistance, risk factors, and mortality from the class of carbapenems qualitatively. The assessment was determined based on the results of antibiotic sensitivity to microbes, risk factors, and mortality from previous studies. Recent review articles on this subject were not yet available. Therefore, the presence of this review is expected to be able to provide complete information regarding the use of carbapenems as a treatment for pneumonia.

Methods

Literature Search

This study is a type of a narrative review. The search for articles in the PubMed and Science Direct databases was carried out in July-August 2020. The articles reviewed discussed the use of carbapenems for pneumonia focusing on resistance, risk factors, and mortality. The keywords used were "Carbapenems", "Pneumonia", "Resistance", and "Risk factors" using the Boolean "AND" operation to combine the search terms.

Selection of Study

We included the publication of the article in the last 10 years, English-language articles, original research, and articles discussed the resistance, risk factors, and mortality of carbapenem use, and excluded non-English articles and the reports.

Article Extraction

Characteristics of the extracted articles described the lead author's name, the year of publication, the number of bacteria isolates, the type of the causative bacteria, the type of pneumonia, the methodology, antibiotic susceptibility testing, the risk factor and mortality assessment, and the type of study.

Results and Discussion

Carbapenem Resistances

Based on the results of a review of 4 research articles on carbapenem resistance in pneumonia found that *A. baumannii*, Enterobacteriaceae such as *Escherichia Coli* (*E. coli*), and *K. Pneumoniae* are pathogens that generally have resistance to carbapenems. Carbapenem resistance was found in patients with Ventilator Acquired Pneumonia (VAP) and Hospital Acquired Pneumonia (HAP).^{23–25} Of a total of 4 studies, one was a prospective study.²¹ One study were retrospective²² and two studies were a multicentre longitudinal study presented in table 1.^{23,24}

Gram-negative bacteria such as *E.coli* have been shown to be resistant to beta-lactam and quinolone antibiotics. Resistance to *E.coli* is due to its ability to produce Extended-Spectrum Beta Lactamase (ESBL), AmpC β -lactamase, mutases in DNA gyrase and topoisomerase mediated by plasmids.²⁶

A.baumannii is also associated with existing infections in hospitals by different resistance mechanisms, including the inactivation of β -lactam antibiotics by β -lactamase, performs multidrug waste pumps against different antibiotic classes, gene transfer mediated by plasmids, integrons, and transposons in aminoglycoside antibiotics and porin mutases.

P. aeruginosa has contributing resistance mechanisms such as overexpression of

sewage pumps, decreased permeability of the outer membrane and mutases of genes that encode porins and other proteins. *P. aeruginosa* can also survive on dry surfaces in hospital facilities such as inhalers and dialysis.

In addition, these bacteria are also mediated by β -lactamase and AmpC β -lactamase so that they are resistant to beta-lactam class antibiotics. The resistance of *P. aeruginosa* to aminoglycosides is caused by the Aminoglycoside Modifying Enzyme (AME), which inactivates aminoglycosides by attaching phosphate, adenylyl or acetyl radicals to the antibiotic molecule, and decreases the binding affinity to its target in bacterial cells.²⁷

The mechanism of antibiotic resistance can be in various ways, including preventing access to antibiotics on the target: decreased permeability and increased antibiotic reflux, gene mutations: changing the target of antibiotics through gene mutations, direct modification of antibiotics: inactivation of antibiotics through enzymes from bacteria.²⁸ Based on various kinds of literature the resistance can be genotype or phenotype, the resistance mechanism of carbapenems is dominated by porin mutase, antibiotic inactivation by enzyme hydrolysis, increased efflux pump expression and mutase mediated by plasmid.

As an empirical therapy for gram-negative bacteria, carbapenem is a member of the β -lactam antibiotic class. It has the main target of PBP (Penicillin Binding Protein). The ring emulates D-Alanyl D-alanine of peptide chains which are normally bound with the PBP that does not form the synthesis of peptidoglycan. The beta-lactam bonds with PBP make the bacteria lysis.³⁰

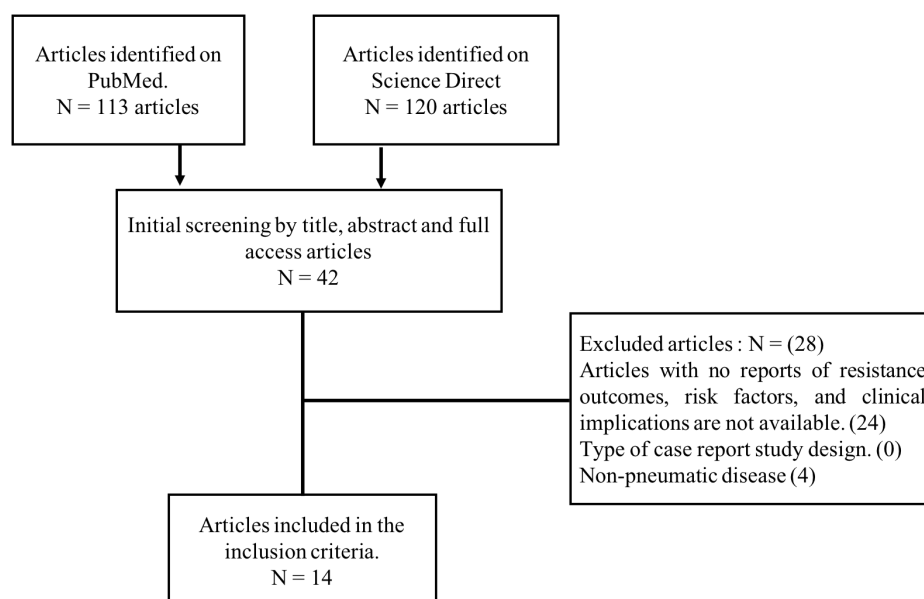


Figure 1. Flowchart of selecting articles. Carabapenems for the treatment of pneumonia: resistance, risk factors, and mortality

*The process of selecting articles from the PubMed and Science Direct search engines. Articles are obtained through an initial screening process based on title, abstract, and full access to articles. Furthermore, the articles were selected based on inclusion and exclusion criteria. The articles included in the inclusion criteria were 14 articles

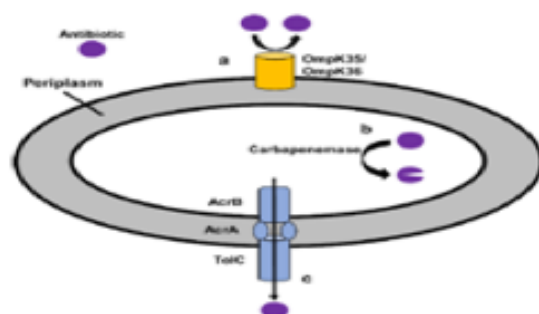


Figure 2. Carbapenem Resistance Mechanism on *Enterobacteriaceae*

a. porin mutation: prevents antibiotics from entering the bacterial cell wall; b. carbapenemase: inactivation of antibiotics by enzyme hydrolysis; c. increase in efflux pump expression; antibiotic efflux²⁹

In general, the occurrence of resistance to beta-lactam (penicillin, cephalosporin, carbapenems, and monobactam) can go through several mechanisms: lack of access to PBP, a reduction in the binding affinity of the PBP, and destruction of antibiotics through lactamase enzymes. Almost gram-positive bacteria (except *staphylococci*) are resistant to beta-lactam antibiotics because of their low affinity for PBP. The gram-negative bacteria are resistant due to the expression of

β -lactamase enzymes such as TEM-1 strains from *E. coli* and SHV-1 from *K. pneumoniae*.

The β -Lactamase enzyme is an enzyme that serves to hydrolyze penicillin, cephalosporins, monobactams, and carbapenems. The bacteria that produce β -lactamases can cause β -lactam antibiotics to be ineffective.^{31,32} There are two classes of β -lactamases namely serine- β -lactamases and Metallo- β -lactamases. The difference lies in its structure where serine-

β -lactamases have a two-domain structure (all α and an α / β), the active site is located between the two domains. The mechanism of breaking the beta-lactam ring is through acylation and deactivation reactions. Metallo- β -lactamases have a four-layer “ $\alpha\beta/\beta\alpha$ ” motif structure, and two α -helices are located on either side. The active sites of Metallo- β -lactamases contain 1 or 2 Zn²⁺ ions, together with metal-binding amino acids and polarized water molecules synergize for hydrolysis of β -lactam antibiotics.³³

Besides due to the hydrolysis of β -lactamase enzymes, carbapenems resistance mechanisms can be through OMP (Outer Membrane Protein), which is the entrance to the release of antibiotics and OMP prevents antibiotics from entering cells. OMP on gram-negative bacteria serves for the absorption of nutrients, adhesive cell, cell signaling, and waste disposal that are not required by bacteria.

In gram-negative bacteria, the OMP of the cell wall is less permeable to many antibiotics, decreases the permeability of the outer membrane, and limits the antibiotic entry into bacterial cells through regulation of porin by replacing porin with a more selective channel. Increased efflux pump expression also plays a role in carbapenem resistance, as a result of which many antibiotics leave the cells. Generally, gram-negative bacteria such as *K. pneumoniae* encode the expression of the KexD gene, mobilization of spread through gene coding in plasmids so that they can move between bacteria.^{29,31,35}

The results on antibiotic resistance presented in the MIC₅₀ and MIC₉₀ values are the lowest concentrations of antibiotics that could inhibit 50% and 90% of bacterial isolates.⁴⁴ The carbapenem values (imipenem, meropenem, doripenem) has experienced some resistance to *A. baumannii*, *P. aeruginosa*, *K. pneumoniae*,

and *Enterobacteriaceae*, which the MIC₅₀ and MIC₉₀ values above the average range ≤ 0.012 -128 ($\mu\text{g/mL}$). Of the three carbapenems tested, the highest concentration of MIC₅₀ and MIC₉₀ values to inhibit gram-negative bacteria is in imipenem proving that it is resistant compared to other carbapenems.^{22,25,36,37}

The widespread carbapenems resistance triggers the presence of risk factors for carbapenems resistance and mortality.^{23,25} The use of carbapenem that has become more widespread has caused risk factors for carbapenem resistance and mortality due to carbapenem resistance. Moreover, it affects treatment outcome, increases the economic burden on patients, and indirectly causes mortality.³¹

Risk Factors and Mortality due to Carbapenem Resistance

The risk factors are a history of carbapenems use, duration of hospitalization, use of mechanical ventilation, high scores of Simplified Acute Physiology Score (SAPS), and Acute Physiologic and Chronic Health Evaluation (APACHE). Carbapenems resistance causes septic shock, high Sequential Organ Failure Assessment (SOFA) scores, and elevated risk at > 60 years of age, female, and inappropriate choice of antibiotics.³⁶⁻⁴⁵

A. baumannii, *P. aeruginosa*, and *Enterobacteriaceae* are gram-negative bacteria that dominate the occurrence of nosocomial infections, especially in surgical wards and ICUs. The types of pneumonia that were significant for gram-negative nosocomial infections were VAP and HAP.^{36-45,46,47} ICU hospitalization, mechanical ventilation, comorbidities, and a history of antibiotic consumption are the risk factors for developing VAP.^{48,49} Similar to VAP, HAP appears due to a history of antibiotic use, especially carbapenems.^{50,51}

Table 1. Results of Antibiotic Sensitivity Test Assessment on Carbapenem Group

Reference	Number of Bacteria Isolates	Causative Bacteria	Type of Pneumonia	Method	Resistance Indicators	Study Type
Kiratisin et al. 2012 ²⁴	1260	<i>A.baumannii</i> <i>P. aeruginosa</i> <i>Enterobacteria-ceae</i>	VAP	Antimicrobial susceptibility testing	MIC50/MIC90 (doripenem, imipenem, and meropenem were: <i>P. aeruginosa</i>: 0.38/8, 1.5/32 and 0.38/16 mg/L <i>Enterobacteriaceae</i>: 0.023/0.094, 0.25/0.5 and 0.032/0.094 mg/L <i>A. baumannii</i> 32/64, 32/128 dan 32/64 mg/L Three carbapenems showed weak activity against <i>A. baumannii</i> . The highest resistance occurred in <i>A. baumannii</i> of 73.0% and <i>P. aeruginosa</i> of 29.8%.	A multicenter study
Le Minh et al. 2015 ²¹	74	<i>A. baumannii</i>	VAP	PCR	Imipenem (82 %) Meropenem (84%) Imipenem = MIC50 and MIC90 (64/64) Meropenem = MIC50 and MIC90 (32/64)	A prospective observational study
Biedenbach D.J et al. 2016 ²³	2402	<i>A. baumannii</i> <i>P. aeruginosa</i> <i>Acinetobacter spesices</i>	HAP or VAP	Broth Microdilution	The resistance of cephalosporins, β -lactam/ β -lactamase inhibitors, carbapenems, and fluoroquinolones > 90% to <i>A. baumannii</i> <i>P. aeruginosa</i> : doripenem (58.6% susceptible) <i>A.baumanii</i>: Doripenem = MIC50 / MIC90 = >4 / > (range 0.12 to 4) Meropenem = MIC50 / MIC90= >8 / >8 (range \leq 0.12 to 8) Imipenem = MIC50 / MIC90= >8 / >8 (range \leq 0.12 to 8) <i>Acinobacter spp</i> : Doripenem = MIC50 / MIC90= >4 / >4 (range 0.12 to 4) Meropenem = MIC50 / MIC90 >8 / >8 (range \leq 0.12 to 8)	A multicenter longitudinal study

Table 1. Results of Antibiotic Sensitivity Test Assessment on Carbapenem Group (cont...)

Reference	Number of Bacteria Isolates	Causative Bacteria	Type of Pneumonia	Method	Resistance Indicators	Study Type
Mao T. et al. 2019 ²²	4	<i>P. aeruginosa</i> <i>E. coli</i> <i>K. pneumoniae</i> <i>A. baumannii</i>	Pneumoniae	Broth Dilution	<i>P. aeruginosa</i> = Meropenem/Imipenem (%) (47.34/56.73), The value of MIC BreakPoint MIC90 (4/4) <i>E. coli</i> = Meropenem/Imipenem (0.9/1.54), The value of MIC BreakPoint MIC90 (2/2) <i>K. pneumoniae</i> = Meropenem/Imipenem (4.95/4.1), The value of MIC BreakPoint MIC90 (2/2) <i>A. baumannii</i> = Meropenem/Imipenem (48.19/46.48), The value of MIC BreakPoint MIC90 (4/4)	A retrospective observational cohort study

Table 2. Assessment Results of Resistance Risk Factors and Mortality due to Carbapenems

Reference	Number of Patients	Causative Bacteria	Type of Pneumonia	Method	Risk Factor	Mortality	Study Type
Zheng, Y. L., et.al 2013 ⁴²	242	<i>A. baumannii</i>	HAP	VITEK	History of antibiotic use within 28 days (carbapenems and cefepime), systemic diseases (chronic respiratory diseases and cerebrovascular accidents), Invasive device (mechanical ventilation)	A score of APACHE II (> 20) when onset pneumonia, infection. Other microorganisms, inappropriate therapy	A retrospective cohort study
Seligman et al. 2013 ⁴⁵	140	<i>S. aureus</i> <i>Enterobacter sp.</i> <i>K. pneumoniae</i> <i>P. aeruginosa</i> <i>E. coli</i> <i>Haemophilus sp.</i> <i>Acinetobacter sp.</i> <i>Coagulase-negative Staphylococcus sp.</i> <i>Enterococcus sp</i>	HAP	Bacteriological Test Results	COPD; congestive heart failure; chronic renal failure; Dialysis; urinary catheterization; Extra-pulmonary infection; and use of antimicrobial therapy within the last 10 days before the diagnosis of HAP	-	A Retrospective observational cohort study
Luyt, C.E., et al, 2014 ⁴³	169	<i>P. aeruginosa</i>	VAP	Disk Diffusion Method, Mueller-Hinton agar and disks of antibiotics	Carbapenem use Mechanical ventilator before onset VAP	A score of SOFA : 7 Dependence on mechanical ventilation day 7	A prospective observational study
Tark, Kim et.al 2014 ⁴⁴	320	<i>A. baumannii</i> <i>P. aeruginosa</i> <i>K. pneumoniae</i> <i>S. aureus</i>	HAP	Microdilution	Diabetes mellitus Radiological Score >5 Previous use of carbapenems and fluoroquinolone	-	A Retrospective multicenter study

Table 2. Assessment Results of Resistance Risk Factors and Mortality due to Carbapenems (cont...)

Reference	Number of Patients	Causative Bacteria	Type of Pneumonia	Method	Risk Factor	Mortality	Study Type
Inchai, J., et.al 2015 ⁴⁰	337	<i>A. baumannii</i>	VAP	Disk diffusion, Mueller-Hinton agar and disks of antibiotics	MDR-AB = previous use of Carbapenems XDR AB = previous use of Carbapenems and SOFA score PDR AB = high the use of colistin, carbapenems, and high SAPS II	-	A retrospective cohort study
de Maio et al. 2016 ³⁶	127	<i>Enterobacteriaceae</i>	Pneumoniae 52 (42%)	Antimicrobial susceptibility testing, PCR, PFGE	-	>60 years old Shock Dialysis Antimicrobial susceptibility testing more than 12 hours Urinary Tract Infection Pneumonia Monotherapy More than two comorbidities	A prospective cohort study
Bal, Z. et.al 2018 ³⁸	27	<i>A.baumannii</i> <i>P. aeruginosa</i> <i>K. pneumoniae</i> <i>Chramobacter xyloxidans</i> <i>Enterobacteriaceae</i>	VAP	Antimicrobial susceptibility testing	Longer hospitalization Previous use of carbapenems	Septic shock	A retrospective observational study
Čiginskienė, et.al 2019 ⁴¹	309	<i>A. baumannii</i>	VAP	Antimicrobial susceptibility testing	MDR, XDR, and PDR = High SAPS II score Longer hospitalization time before entering the ICU Mechanical ventilation The use of Carbapenems	Female gender SOFA score when in ICU RBC transfusion	A retrospective observational study

Table 2. Assessment Results of Resistance Risk Factors and Mortality due to Carbapenems (cont...)

Reference	Number of Patients	Causative Bacteria	Type of Pneumonia	Method	Risk Factor	Mortality	Study Type
Liu, W. D., et.al 2019 ³⁹	309	<i>Enterobacteriaceae</i> <i>NFGNB (Non-Fermenting Gram Negative Bacteria)</i> <i>Others: MRSA dan Enterococcus</i>	VAP/HAP	Antimicrobial susceptibility testing	-	Solid-organ Malignancy Score SOFA	A retrospective observational study
Choe, Y. J. et al. 2019 ³⁷	74	<i>A. baumannii</i>	Pneumoniae	Antimicrobial susceptibility testing	-	Unsusceptible Carbapenems Neutropenia Before in ICU	A Retrospective study

Table 3. Results of study on Other Therapeutic Options for Gram-Negative Bacteria

Reference	Bacteria	Comparative Antibiotics	Reccomendation
Cheng, A. et al.2015 ⁶¹	XDR <i>A. baumannii</i>	Colistin-Tigecycline vs Colistin -Carbapenems	Colistin - Carbapenem
Ku, Y. H. et al.2017 ⁶²	ESBL producing <i>K. Pneumoniae</i>	Colistin – Tigecycline vs Tigecycline – Fosfomycin	Colistin - Tigercycline
Paul, M. et al 2018 ⁶³	Carbapenems-Resistant Gram-Negative Bacteria (<i>A. baumannii</i>)	Colistin Vs Colistin - Meropenem	Combination therapy is not superior to monotherapy
Van Duin, D. et al. 2018 ⁵¹	Carbapenems-Resistant <i>Enterobacteriaceae</i>	Colistin Vs Seftazidim – Avibactam	Ceftazidime – Avibactam
Cisneros, J. M. et al.2019 ⁶⁴	Carbapenems-Resistant Gram-Negative Bacteria	Colistin Vs Meropenem Colistin-Levofloksasin Vs Meropenem-Levofloksasin	Treatment of colicin versus meropenem or the combination of both did not show inferiority
Yu, L. et al.2019 ⁶⁵	Carbapenems-Resistant <i>K. Pneumoniae</i>	Colistin-Amikasin Colistin-Meropenem	Both combination can be an alternative

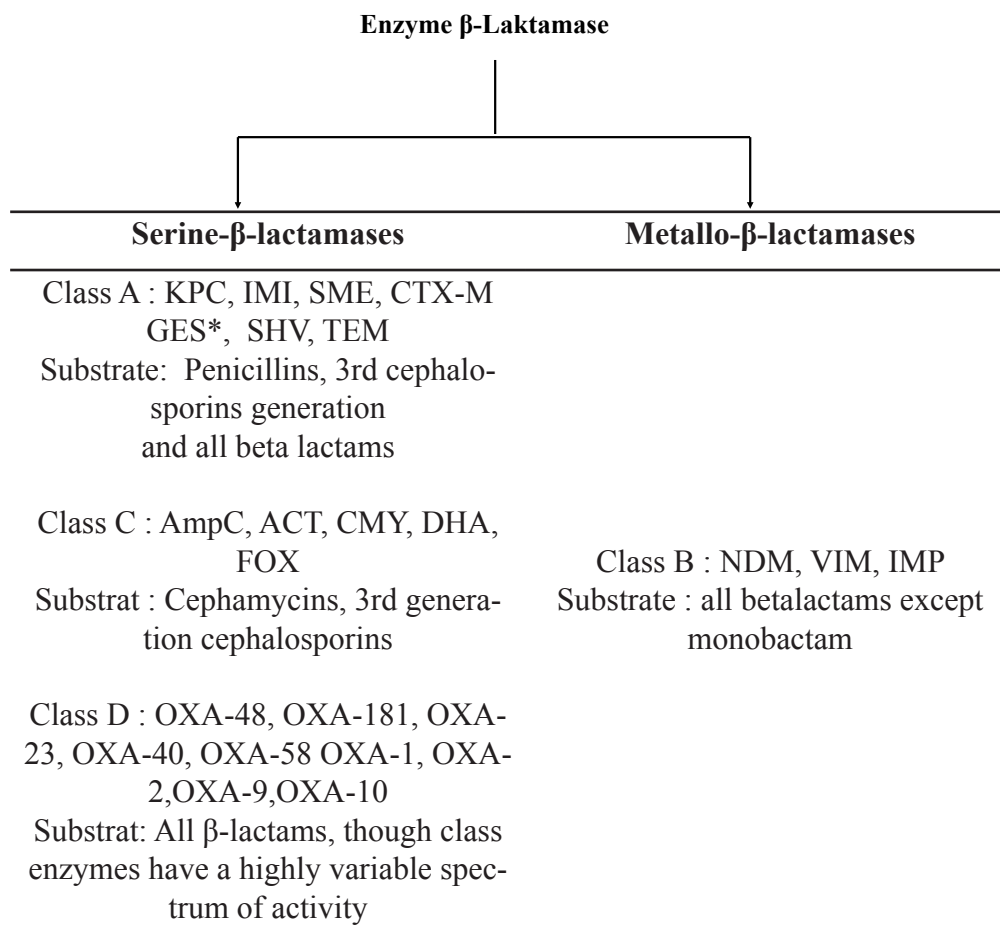


Figure 3. The Classification of the β -lactamase Enzyme depends on its Central Catalytic Domain^{29,34}

Classification of carbapenemases/ β -lactamases depending on their central catalytic domain. Abbreviations: ACT, AmpC type β -lactamase; AmpC, ampicillin chromosomal cephalosporinase; CMY, cephamycin-hydrolyzing β -lactamase; CTX-M, cefotaxime-hydrolyzing β -lactamase–Munich; FOX, plasmid-mediated class C β -lactamase; GES, Guiana extended-spectrum β -lactamase; IMI, imipenem-hydrolyzing β -lactamase; IMP, imipenemase Metallo- β -lactamase; KPC, Klebsiella pneumoniae carbapenemase; NDM, New Delhi Metallo- β -lactamase; OXA, oxacillin carbapenemase/oxacillinase; SHV, sulfhydryl variant of the TEM enzyme; SME, Serratia marcescens enzyme; TEM, Temoneira class A extended-spectrum β -lactamase; VIM, Verona integron-encoded Metallo- β -lactamase.

The previous use of carbapenems makes bacteria resistant, resulting in unsusceptible strains.⁵² According to the Infectious Disease Society of America (IDSA), the risk factors for MDR (Multi-Drug Resistant) in VAP are the previous use of intravenous antibiotics within 90 days, septic shock during VAP, acute respiratory distress syndrome before VAP, five or more days of hospitalization before the onset of VAP, replacement therapy of acute kidney before the onset of VAP. Meanwhile, the risk factor for MDR in HAP is the previous use of intravenous antibiotics within 90 days.⁵³

The association of risk factors with the incidence of carbapenem resistance can be due to the patient's longer stay in hospital, where the patient may be receiving invasive treatment or antibiotic treatment for a longer period of time or with a broad spectrum.⁵⁴ These bacteria may be intrinsically resistant to antibiotics causing the proliferation of strains to antibiotics and making them dominant.⁵⁵

Another risk factor is the use of mechanical ventilation which triggers the risk of VAP arising from aspiration of infected secretions

from the oropharynx, direct infection of the blood, or colonization of the oropharynx. Endotracheal tube insertion breaks down natural defence mechanisms such as cough reflex and mucociliary clearance, and causes direct interaction between the oral supraglottis space and the lower respiratory tract.⁵⁶

Risk factors for high SAPS and APACHE scores are a factor in the emergence of carbapenems resistance. Pneumonia is potential to cause sepsis if the antibiotics treatment is not able to kill bacteria causing dysfunction to organ which leads to mortality. Many factors can lead to mortality including length of hospitalization, concomitant condition, and previous use of antibiotics.⁵⁷ Besides, the clinical implications of carbapenem resistance can exacerbate the patient's condition such as a higher APACHE score, prolonged hospitalization time, higher comorbidity, and anemia. Various studies regarding the clinical implications of explaining the type of pneumonia that is often obtained are HAP.⁵⁸⁻⁶⁰

Antibiotic Options to Overcome Carbapenem Resistance

Other selection of antibiotic therapy as an alternative to overcome resistance to carbapenem antibiotics presented in Table 3.^{51,61-65} The threat of resistance and mortality due to some carbapenems-resistant gram-negative bacteria results in the discovery of monotherapy or combination therapy, such as colistin-tigecycline, colistin-carbapenem.⁶¹ Colistin-tigecycline combination synergized in eight isolates and six isolates had bactericidal activity compared to the less active tigecycline - fosfomycin (only four isolates showed synergy and no bactericidal activity).⁶²

The combination of colistin - meropenem and colistin monotherapy showed no difference in improving clinical symptoms caused by *A.*

baumanii infection.⁶³ The same result from the study of Cisneros, J.M et.al., 2019 showed non-inferiority results between colistin versus meropenem and both when combined with levofloxacin on VAP patients.⁶⁴ Later studies assessed the synergy of the colistin-amikacin/meropenem combination as a therapeutic option for CRKP (*Carbapenem-resistant Klebsiella pneumoniae*) infection that has been resistant to colistin.⁶⁵ Monotherapy regimen or a combination of colistin, cephalosporin, and carbapenems can be other therapeutic options when patients are resistant to carbapenem. According to the IDSA, alternative therapies for carbapenems resistance based on VAP and HAP treatment management, adapt to each hospital's germ sensitivity pattern and the microbial susceptibility associated with the type of pneumonia while considering possible side effects.⁴⁸

Standards for Infection Prevention and Control

The standard for infection prevention and control carried out by health facilities according to the Centers for Diseases Control and Prevention (CDC) are controlling infection that transmit to air, water, environment, laundry and bedding, and especially for the control of infections caused by pneumonia-causing bacteria, there are guidelines recommended by the CDC. Pneumonia in health facilities can spread easily by spreading through the use of tap water given directly to patients during treatment, or diluting solutions, ventilators, gloves and hand hygiene.

Prevention and control to gram-negative bacteria in the hospital can be done by providing disinfectant regularly in the room, arranging for air circulation in and out, keeping toilets clean, providing hand hygiene in a place that is easily accessible, equipment must be dry, adding germicides in it, water, and etc. Apart from maintaining a clean

environment, hospitals and other facilities can also measure the pattern of germs present in their respective facilities by monitoring the sensitivity of antibiotics to the tested bacteria. Assessment of germ patterns and antibiotic sensitivity also functions to administer the empiric antibiotics, which are antibiotics that are given before definitive antibiotics against a certain infection. Authors have observed that the standards for infection prevention and control in health care facilities are good, however, there may be a need for more routine outreach, especially for the patients and the visitors.^{66,67}

Conclusion

The analyzed studies of 14 articles report that carbapenems are resistant to gram-negative bacteria. Of the variations of carbapenems tested, imipenem is the most resistant among other variations of carbapenems tested. The risk factors that dominated the causes of resistance are earlier carbapenems usage and the cause of mortality due to carbapenems resistance in septic shock. Based on the results of the review, we concluded that colistin can be used as an alternative treatment when patients are resistant to carbapenems against the gram-negative bacteria that causes pneumonia. The germ patterns in each tertiary service facility are taken into consideration for this choice. The author expects that through this study the reader can understand the rational use of antibiotics, especially carbapenems and minimize the risk factors for the emergence of resistance.

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Conflict of Interest

None declared.

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