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RESEARCH ARTICLE

A Narrative Review: Evaluation of Resistance Antibiotics used in Pneumonia

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ABSTRACT:

Background: According to the World Health Organization, lower respiratory tract infection such as pneumonia is in the category of ten leading causes of death in global. Many antibiotics used as the first-line treatment for pneumonia, such as penicillin and cephalosporins, are reported to be resistant. This review aimed to evaluate the resistance of antibiotics used for the treatment of pneumonia in order to provide information about antibiotic resistance. Thus, it can be a consideration for choosing the right antibiotic. **Method:** This paper was reviewed from previous research on antibiotic resistance used for the treatment of pneumonia using a search engine on the PubMed and Science Direct databases from 2011 to 2021. The articles assessed reported resistance from various classes of antibiotics such as macrolides, quinolones, carbapenems and aminoglycosides based on inclusion criteria. and exclusion. **Result:** Of the 19 articles included in the inclusion criteria, they were reported about resistance to macrolides that they found A2063G mutations in the 23S rRNA gene, quinolones resistance was found to be gyrA and ParC mutations, carbapenems resistance was assessed by high MIC and found in the $bla_{\text{OXA-51}}$, $bla_{\text{OXA-23}}$ and $bla_{\text{NDM-}}$ genes as the gene encoding the lactamase enzyme and porin mutation. Resistance to aminoglycosides found AAC (6′)-Ib mutations on the 16S rRNA gene. **Conclusion:** Based on the results of the study, generally all classes of antibiotics used to treat pneumonia are resistant. To overcome antibiotic resistance, the use of combination antibiotics and increased doses are prescribed.

KEYWORDS: Resistance, Evaluation, Antibiotics, Pneumonia, Gram-negative bacteria.

INTRODUCTION:

Pneumonia is a type lower respiratory tract infection caused by microorganisms such as bacteria, viruses or fungi. Pathologically, the invasion of microorganisms enters the alveoli in large numbers. They cause an inflammatory response from the host cell. Access to microorganisms to reach the lower respiratory tract can be through inhalation, aspiration, direct inoculation, and haematogenous. For initial defence, the body will fight invading microorganisms. If the host body's defences are low accompanied by an uncontrolled inflammatory response, it will cause septic shock and organ failure which can lead to death.[1–3]

Based on United Nations Children's Fund (UNICEF) in 2019, 84% children's deaths due to pneumonia occurred in 30 countries. Low-income countries have a 60 times higher risk of death than high-income countries. The incidence of pneumonia cases in children in the world in developing countries in Asia such as India, Nigeria, Indonesia, Pakistan, and China reached more than 54%, in which 32% came from India.[4] For treatment of pneumonia requires antibiotics as the main therapy.

According to the previous research, it reported antibiotic resistance of the beta-lactam class, especially penicillin and cephalosporins for the treatment of pneumonia, has experienced a lot of resistance. However, in the current era, various resistances from other antibiotic classes such as carbapenems, macrolides, quinolones and aminoglycosides start to have resistance.[5–8] Antibiotic resistance in pneumonia generally comes from Gram-

negative bacteria such as *Acinobacter baumanii*, *Pseudomonas aeruginosa*, *Klebsiella pneumoniae* and *Enterobacteriaceae* that can cause serious therapeutic problems.[9–12] Resistance of various antibiotic classes is caused by overuse of antibiotics, inappropriate prescribing, administration of antibiotics to livestock, lack of availability of new antibiotics and regulatory barriers to issuing new antibiotics.[13,14,15] Problems due to resistance have an effect on patient recovery, for example from several studies on resistance to macrolides that have clinical implications for patients, the consequences of resistance to macrolides can prolong the length of stay and worsen symptoms and complications.[16–21]

This review aimed to evaluate the resistance of antibiotics used for the treatment of pneumonia in order to provide information about antibiotic resistance. Thus, it can be a consideration for choosing the right antibiotic in the treatment of pneumonia. The objective assessment is based on the variation in the results of the analysis of resistance from various antibiotic classes in previous studies.

MATERIALS AND METHODS:

Literatur Search:

This type of review is a narrative review. The article used in this review discussed antibiotics used to treat pneumonia with a focus on resistance. The search for articles in the PubMed and Science Direct databases was conducted in July-August 2020. The keywords used were "Resistance", "Pneumonia", ”Carbapenems", "Macrolides", "Quinolones" and "Aminoglycosides" using the Boolean "AND"operation to combine search terms.

Selection Study:

Articles were selected through inclusion and exclusion criteria. For inclusion criteria: publication restrictions had been carried out in the last 10 years, in English, the articles were original research, the subject was bacterial isolates. Articles that were reports and case series were issued. **Article Extraction.** The characteristics of the extracted articles had the name of the main author, the year of publication, the type of study, the pathogen causing pneumonia, the number of bacterial isolates, the method, the antibiotic susceptibility results. From 415 articles obtained (299 from PubMed and 116 from Science Direct), the articles were excluded based on the title and abstract. Thus, 38 articles were obtained to be assessed for their proper text completeness. Nineteen articles were excluded because they did not report the data required for review. The total inclusion criteria obtained were 19 articles. Of the nineteen articles, reporting on the antibiotic resistance of macrolides, quinolones, carbapenems and aminoglycosides are presented in Table 1.

RESULT:

Table 1. Antibiotic Resistance of Macrolides, Quinolones, Carbapenems, Aminoglycosides

S. No	Reference	Pneumonia type	Number of Bacterial Isolates	Causative Pathogens	Resistance Indicator
Macrolides					
1.	Eshagi *et.al* 2013[22]	CAP	115	*M.pneumoniae* and *Chlamydophila pneumoniae*	A2063G and A2064G mutations in the 23S rRNA gene (Erythromycin MIC > 64 mg / L)
2.	Wu, H. M *et.al* 2013 [17]	CAP	9	*M. pneumoniae*	A2063G mutation in the 23S rRNA gene
3.	Zhang W.Z *et.al* 2019 [16]	CAP	19	*M.pneumoniae*	A2063G mutation in the 23S rRNA gene
4.	Meyer Sauteur *et.al* 2015[18]	CAP	50	*M. pneumaoniae*	A2063G mutation in the 23S rRNA gene
5.	Ferguson, G. D.*et.al* 2013[23]	HAP	307	*M. pneumoniae*	23S rRNA gene mutation
6.	Hong, K. B. *et.al* 2013[24]	HAP	80	*M. pneumoniae*	A2063G and A2064G mutations in the 23S rRNA gene
7.	Ishiguro, N. *et al* 2016[25]	HAP	51	*M. pneumoniae*	A2063G mutation in the 23 rRNA gene
8.	Katsushima, Y. *et al.* 2015[26]	CAP	27	*M. pneumoniae*	A2063G and C2617G mutations in the 23 rRNA gene
9.	Ma, Z *et al*. 2014[27]	HAP	36	*M. pneumoniae*	A2063G and A1290G mutations in the 23 rRNA gene
Quinolones					

1.	Takeuchi, N. *et al.*2017 [28]	HAP	2	*S.pneumoniae*	Tosufloxcacin -resistant MIC_{90} ≥ 2 mg/L
2.	Nakai, H. *et al.* 2018 [29]	CAP	92	*S.pneumoniae* *H.influenzae* *M.catarrhalis*	MIC_{90} levofloxacin 0.781 µg /mL *S. pneumoniae* 0.049 µg/mL *M.catarrhalis.* (considered to be resistant If > 2µg / mL) It is found (gyrA and ParC,)
3.	Schmitz, J. *et al* 2017 [30]	Pneumonia	52	*S.pneumoniae*	It is found gyrA, gyrB and ParC, parE
Carbapenems					
1.	Le Minh *et al.* 2015 [31]	VAP	74	*A. baumannii*	Imipenem = MIC50 and MIC_{90} (64/64) Meropenem = MIC50 and MIC_{90} (32/64) Resistance gene = bla_{OXA-51}, bla_{OXA-23} and bla_{NDM-1}
2.	Mao T. *et al.* 2019[32]	Pneumonia	4	*K. pneumoniae* *E. coli* *P. aeruginosa* *A. baumannii*	*P. aeruginosa* = Meropenem / Imipenem (47.34 / 56.73), Break Point MIC Value MIC_{90} (4/4) *E. coli* = Meropenem / Imipenem (0.9 / 1.54), Break Point MIC Value MIC_{90} (2/2) *K. pneumoniae* = Meropenem / Imipenem (4.95 4.1), Break Point MIC Value MIC_{90} (2/2) *A.baumann*i = Meropenem / Imipenem (48.19/46.48), MIC value Break Point MIC_{90} (4/4)
3.	Biedenbach D.J *et al*. 2016 [33]	HAP Atau VAP	2.404	*A. baumannii* *P. aeruginosa* *Acinetobacter spesices*	Carbapenems for *A.baumanii* bacteria: Doripenem = MIC_{50} / MIC_{90} => 4 /> 4 (range 0.12 to 4) Meropenem = MIC_{50} / MIC_{90} => 8 /> 8 (range ≤ 0.12 to 8 Imipenem = MIC50 / MIC90 => 8 /> 8 (range ≤ 0.12 to 8 Carbapenems for *Acinobacter* spp: Doripenem = MIC_{50} / MIC_{90} => 4 /> 4 (range 0.12 to 4) Meropenem = MIC_{50} / MIC_{90} > 8 /> 8 (range ≤ 0.12 to 8 Imipenem = MIC_{50} / MIC_{90} => 8 /> 8 (range ≤ ≤ 0.5 to 8 Carbapenems for *P. aeruginosa*: Doripenem = MIC_{50} / MIC_{90} = 1 /> 4 (range ≤ 0.06 to> 4) Meropenem = MIC_{50} / MIC_{90} = 1 /> 8 (range ≤ 0.12 to 8 Imipenem = MIC50 / MIC90 = 4 /> 8 (range ≤ 0.5 to 8
4.	Kiratisin *et al.* 2012 [34]	VAP	1.260	*A. baumannii* *P. aeruginosa* *Enterobacteriaceae*	MIC_{50} / MIC_{90} (doripenem, imipenem and meropenem were: 0.38 / 8, 1.5 / 32 and 0.38 / 16 mg / L for *P. aeruginosa*; 0.023/0.094,0.25/0.5 and 0.032/0.094 mg / L for *Enterobacteriaceae*; and 32/64, 32/128 and 32/64 mg / L for *A. baumannii*
Aminoglycosides					
1.	Mózes, J. *et al.* 2014 [35]	Pneumonia	98	*P.aeruginosa*	It was found genes aac (6 ′)-Ib and ant (2″) – Ia
2.	Nasiri, G. *et.al* 2018 [36]	HAP	177	*K.pneumoniae*	It was found aac (6′) - Ib, aac (3) -II (78.5%), aph (3") - IIIa (14.6%), ant (4') - Ia (3.1%), and armA (7.7%)) genes
3.	Nie, L. *et al* 2014 [37]	HAP	102	*A.baumanii*	It was found (3″) - I, aac (3) - I, aph (3 ') - I, aac (6') - Ib, aac (3) -IIc, aac (6 ') - II and aph (3') – Iib genes It was found HLAR ant (3 ″) - I, aac (3) -I, aph (3 ') - I, aac (6') - Ib and aph (3 ') - IIb

PCR: Polymerase Chain Reaction, qPCR: Quantitative Polymerase Chain Reaction, RT-PCR: Real Time Polymerase Chain Reaction, PFGE: Pulsed-Field Gel Electrophoresis, MIC: Minimum Inhibitory Concenteration, *M. pneumoniae*: *Mycoplasma pneumoniae*, *H.influenzae*: *Haemophilus influenzae*, *M.catarrhalis*: *Moraxella catarrhalis*, *A.baumanii*: *Acinobacter baumanii*, *P.aeruginosa*: *Pseudomonas aeruginosa*, *E.coli* : *Escheria coli*, *K.pneumoniae* : *Klebsiella pneumoniae*, HLAR : High Level Aminoglycosides Resistance, CAP : Community Acquired Pneumonia, HAP : Hospital Acquired Pneumonia.

As antibiotic resistance was found in the treatment of pneumonia, some researchers are looking for alternative antibiotics to improve the therapeutic outcome to make it more effective. The following are some researches regarding the comparison of antibiotics for the treatment of pneumonia presented in Table 2.

Table 2. Results of study on Other Therapeutic for Bacteria Causes Pneumonia

S. No	Reference	Comparative Antibiotics	Recommendation
Macrolides			
1.	Ishiguro, N. *et al* 2017[38]	Azithromycin vs clarithromycin vs tosufloxacin vs minocycline	Minocycline is more effective
2.	Kawai, Y. *et al.* 2013[39]	Azithromycin vs clarithromycin vs tosufloxacin vs minocycline	Minocycline is more effective
3.	Skalsky, K. *et al.* 2013[40]	Macrolides vs quinolones	Quinolones
4.	Teh, B *et al.* 2012[41]	Macrolides vs Doxycycline	Doxycycline
Quinolones			
5.	Safarika, A. *et al.* 2014[42]	Quinolones + Imipenem + colistin	Levofloxacin can be used as combination therapy: Quinolone + colistin
Carbapenems			
6.	Cheng, A. *et al.*2015[43]	Colistin-Tigecycline vs Colistin - Carbapenems	Colistin – Carbapenems
7.	Ku, Y. H. *et al.*2017[44]	Colistin – Tigecycline Vs Tigecycline – Fosfomycin	Colistin – Tigecycline
8.	Dickstein Y. *et al* 2018[45]	Colistin Vs Colistin – Meropenem	Combination therapy is not superior to monotherapy
9.	Cisneros, J. M. *et al.*2019[46]	Colistin Vs Meropenem/ Colistin-Levofloksasin/ Vs/Meropenem-Levofloksasin	Treatment of colicin versus meropenem or the combination of both did not show inferiority
10.	Yu, L. *et al.*2019[47]	Colistin-Amikasin/ Colistin-Meropenem	Both combination can be an alternative
11.	Van Duin. *et.al* 2018[48]	Colistin Vs Ceftazidime – Avibact	Ceftazidime – Avibactam
Aminoglycosides			
13.	Tamma *et.al* 2012[49]	Beta-lactam + Aminoglycosides	Both combinations can be an alternative

DISCUSSION:

A. Resistance to Macrolides:

Macrolides are a class of antibiotics used to kill pneumonia-causing bacteria such as *S. pneumoniae*, *Haemophilus influenzae*, *M. catarrhalis* and atypical bacteria such as *Legionella pneumophila*, *M. pneumoniae*, *Chlamydia pneumoniae*, shigellosis, and salmonellosis. This class of antibiotics is the mainstay of therapy for pneumonia in children. Macrolide antibiotics have a mechanism of action by inhibiting protein synthesis by targeting ribosomes from bacteria by binding 23S rRNA to the 50S ribosomal subunit downstream from the centre of peptydiltransferase as a peptide bond forming. Hence, the newly formed protein will not come out in the Peptide Exit Tunnel (PET).[50,51] From the 9 literatures studied, resistance to macrolides is dominated by chromosomal mutations in the 23S rRNA gene at position 2063 with changes in the position of purine bases A to G in *M. pneumoniae* bacteria that were found in the population was mostly children. The occurrence of in the mutation 23S rRNA gene has been shown to correlate with the incidence of resistance to macrolide antibiotics.[52] The mechanism of genetic resistance in the macrolides group is through changes in the ribosome target, such as 23S rRNA methylation and mutations in the 23S rRNA gene. In 23S rRNA methylation, especially adenine 2058 that play a role in binding macrolide antibiotics, methylation is encoded by the Erm gene (Erythromycin ribosome methylase) as gene expression that can induce and regulate attenuation or continuous translation. The Erm B gene is the most common gene to dominate the resistance to macrolides of *S.pneumoniae*. Monomethylating on A2058 provides a low level of resistance to erythromycin, whereas demethylation causes high resistance.[53,54] In gene mutations, in which the amino acid adenosine to guanine changes, resistance to macrolides has been associated with mutations at sites 2063, 2064, 2067, and 2617 V domain of 23S rRNA. The A2063G transition is the most common mutation found in resistance macrolides, followed by the A2064G transition.[19,21] From various other researches besides the amino acid position of 2063, there were also 2617 and 2067 that had mutations.[22,23,35] Likewise, from reports originating from China, 70 isolates *M.pneumoniae* resistant pneumonia with a Minimum Inhibitory Concentration (MIC) value of erythromycin 32-512 mg/L and showed mutations at the site of 2063 or 2064 in domain V of 23S rRNA.[55]

B. Resistance to Quinolones:

Quinolones are antibiotics that have broad-spectrum activity against Gram-negative and Gram-positive bacteria. New generation of fluoroquinolones such as levofloxacin, moxifloxacin, and sparfloxacin are

effective against Gram-positive compared to first generation quinolones. Fluoroquinolones have better pharmacological properties with lower MIC, greater penetration to tissue and a wider spectrum.[56,57] Several studies reporting found target-mediated resistance such as mutation of the gyrA gene, gyrB , ParC and ParE on test bacteria of *S.pneumoniae*, *H.influenzae M.catarhalis*. The MIC value of quinolones antibiotics is considered to be resistant to $MIC_{90} \geq 8\mu g/ml$, intermediate $MIC_{90} \geq 2\mu g$ /ml - $MIC_{90} \geq 8\mu g$ / ml.[28–30,58] Quinolones have a target of inhibiting two essential enzymes in bacteria that play a role in DNA replication, such as the enzyme gyrase and topoisomerase IV. Gyrase enzyme consists of two subunits GyrA and 2 GyrB and topoisomerase IV consists of two subunits ParC and ParE. GyrA is homologous with ParC, and GyrB is with ParE. The work of the gyrase and topoisomerase enzymes is to catalyse the DNA strand into another double DNA strand, and reseal, in other words, the two enzymes play a role in DNA replication, transcription and translation. Based on the structure of bacteria, quinolones antibiotics have different work targets between Gram-negative and positive bacteria, in Gram-negative the main target is gyrase, while in Gram-positive the main target is topoisomerase IV.[59,60,61] Resistance mediated by target blocks double strand DNA re-sealing, inhibits enzyme activity and stabilizes covalent complexes between catalytic enzymes and DNA. It serves as a barrier to fork and cans movement in DNA replication to breakdown of double-stranded DNA, that correlates with the bactericidal activity of quinolones. Besides, to target-mediated resistance, there is resistance mediated by plasmids known as Plasmid-Mediated Quinolone Resistance (PMQR). those genes are Qnr proteins such as QnrA, QnrB, QnrS, QnrC, and QnrD, a waste pump. active (especially the QepA and OqxAB pumps) and the modified drug AAC (6 ')-Ib-cr *Acetyltransferase*. These resistance genes were inserted into integrins type sul1.[59,62–64] Distribution of resistance genes mediated by plasmids especially in *K. pneumoniae* are *(qnrA1, qnrA3, qnrB1, qnrB2, qnrB6, qnrB1, qnrS19), E.coli (qnrA1, qnrB19, aac (6 ') - Ib-cr, qepA1, qepA2, oqxAB.*[65] Chromosome-mediated resistance such as under-expression of porin and overexpression of efflux pumps play a role in quinolones resistance. Porin expression has function as a selective filter for nutrients needed by bacteria. Intrinsic defence by bacteria through porin adapts to the environment and controls solute permeability. Types of porin expression that affect quinolones resistance against *K.pneumoniae* are OmpK35 and OmpK36. The efflux pump prevents the accumulation of intracellular toxic compounds, the bacteria develop a system that depends on energy to pump molecules out of the cell. The types of efflux pumps that play a role in quinolones resistance in *A.baumanii* bacteria are (AdeABC, AdeFGH, AdeIJK), *E.coli* (AcrAB, AcrAD), *K. pneumoniae* (AcrAD), and *P.aeruginosa* (MexAB-OprM, MexCD- OprJ).[60] The presence of porin expression and overexpression of the bacterial efflux pump can alter the enzyme target and its affinity for drug binding, resulting in reduced levels of accumulated drug due to decreased absorption or increased drug excretion.[54] Along with the resistance found in quinolones, to overcome this problem, quinolones administration is carried out in combination with other antibiotics. From the Safarika A. *et.al* 2014 research, it compared the time-kill effect of levofloxacin combined with imipenem and colistin to fight *P.aeruginosa* and *A.baumanii* Multi Drug Resistant (MDR) bacteria that did not depend on the MIC value of levofloxacin. From other literature sources also reported that pseudomonal infection is also susceptible to colistin.[42,66]

C. Resistance to Carbapenems:

Carbapenems are the member of β-lactam antibiotics whose activity is time-dependent and broad-spectrum. The mechanism of action of carbapenems is by binding to penicillin binding protein (PBP) to prevent transpeptidation thereby inhibiting the synthesis of cell wall bacteria. Of the four literature studied, Gram-negative bacteria such as *A.baumanii*, *K. pneumoniae* and *P.aeruginosa* are pathogens that have generally been resistant to carbapenems. Imipenem is the most resistant compared to other carbapenems groups based on MIC value data. The value of MIC is a measure to predict microbial susceptibility, the imipenem studied had an MIC level of ≥ 4 mg/L. It indicates that the carbapenems were resistant to an intermediate level.[27-30,57,10,67] In general, the resistance mechanism is through enzymatic and non-enzymatic hydrolysis pathways. For enzymatic hydrolysis pathways such as inactivation of antibiotics by the β-Lactamase enzyme, while non-enzymatic pathways such as porin mutations (such as OprD and CarO on carbapenems) and increased expression encoding efflux pumps (such as MexAB-OprM, MexXY-OprM, or MexC ID-OprJ), especially in *P. aeruginosa*.[68–70]

PBP is involved in the formation of bacterial cell walls. Carbapenems antibiotics are a beta-lactam group that have a beta-lactam ring structure. It mimics the structure of D-alanyl D-alanine, that is a catalyst for the biosynthesis of peptidoglycan precursors that normally bind to PBP. Thus, bacterial cell wall synthesis is not formed. As a result, there is inhibition of peptidoglycan synthesis, cessation of cell division and bacteria become lysis. Genes encoding beta-lactamase enzymes are $_{bla}$OXA-51, $bla_{\text{OXA-23}}$, $bla_{\text{NDM-1}}$, bla_{KPC}, bla_{IMP}, $bla_{\text{CTX-M}}$, bla_{TEM}, bla_{SHV}, bla_{OKP} and $bla_{\text{AmpC.}}$ The spread of resistance genes is caused by horizontal gene transfer.[71] The resistance to the beta-lactam antibiotic class differs

between Gram-positive and Gram-negative bacteria. Gram-negative bacteria are generally more resistant to a large number of antibiotics and chemotherapy agents than Gram-positive bacteria due to cell wall differences, decreased external membrane permeability, efflux pumps and the presence of a wide spectrum of β-lactamases such as Extended Spectrum Beta-lactamase (ESBL) and AmpC cephalosporinases. Resistance of Gram-positive bacteria (except staphylococci that produce narrow-spectrum penicillinase) in the beta-lactam group generally has a low affinity for enzymatic-influenced PBP, whereas Gram-negative bacteria generally experience resistance due to changes in PBP, β-lactamase production, and target expression limited access to PBP. The location of the PBP in the periplasmic space of Gram-negative bacteria. Hence, the carbapenems antibiotics must cross the outer membrane of the bacteria to reach its target of action. To cross the periplasmic space, carbapenems may not reach their work target because of the porin loss or efflux pump in Gram-negative bacteria. This also creates the potential for antibiotic cross-resistance.[69,70,72–74] Gram-negative bacteria have three layers of cell walls. The first layer is the Outer Membrane (OM), as layer that functions as a protector. Thus, it distinguishes it from Gram-positive bacteria. Inside OM, there is also an Outer Membrane Protein (OMP) that allows small molecules such as amino acids and saccharides to enter. The second layer is the peptidoglycan cell wall, and the third layer is the Inner Membrane (IM). Antibiotics cross the outer membrane to access their target, in hydrophobic antibiotics enter the membrane through the diffusion pathway, in hydrophilic antibiotics enter through the porin pathway. In Gram-negative bacteria, the outer membrane layer can change due to mutations in porin or other factors. Gram-positive bacteria do not have this such layer, so resistance is more common in Gram-negative bacteria.[75]

Besides being caused by the hydrolysis of the β-lactamase enzyme, the non-enzymatic pathway is through a decrease in the permeability of Outer Membrane Protein (OMP). OMP is the outermost membrane that functions for nutrient absorption, cell adhesion, cell signalling and disposal of waste that is not needed by bacteria. OMP is the door that regulates the regulation of antibiotics into cells. In Gram-negative bacteria, the outer membrane 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 more selective channels. Therefore, many antibiotics leave the cells.[44,69,73] Currently, there are recommendations for therapy of choice to overcome carbapenems resistance. From several studies that colistin, they can be a therapeutic option both in combination and monotherapy. The combination therapy studied compared colistin in combination with tigercycline, meropenem and levofloxacin with mixed results. From the results of the research reviewed, it can be concluded that colistin is an antibiotic whose effectiveness is better than carbapenems to overcome carbapenems resistance in Gram-negative bacteria.[43–46]

D. Resistance to Aminoglycoside:

Aminoglycosides have the potential to fight pathogens from the *Enterobacteriaceae* group including *E. coli* and *K. pneumoniae*. The mechanism of action of aminoglycosides is by inhibiting protein synthesis with high affinity bonds to site-A in 16S ribosomal RNA which is part of the small subunit of the 30S ribosome.[76] Clinical use of aminoglycosides is used as empirical and definitive therapy for serious infections such as severe and nosocomial sepsis. Aminoglycosides can also be combined with second-line antibiotics for their use. Aminoglycosides have strong bactericidal activity so that this antibiotic has relatively low resistance compared to other groups.[77] From the three literature studied, types of bacteria are like *P.aeruginosa*, *K. pneumoniae* and *A.baumanii* isolates are found as causes of aminoglycosides resistance. The gene mutation variant that dominates the occurrence of aminoglycosides resistance is AAC (6′)-Ib. Research originating from Iran reported that *A.baumanii* has the dominant AACC1 gene in coding for aminoglycosides-converting enzymes.[35–37,78]Genes AAC (6′)-Ib (Aminoglycosides 6-N-Acetyltransferase type Ib) is a protein determinant of Plasmid-Mediated Quinolone Resistance (PMQR) a variant of the aminoglycosides resistance enzyme. AAC (6') - Ib with an extended acetylation spectrum provides a low level of resistance to ciprofloxacin and norfloxacin.[79]

Resistance mechanism to aminoglycosides can be carried out through several mechanisms, such as ribosome mutation, 16S rRNA methylation, enzyme modification by Aminoglycosides Modifying Enzyme (AME), and efflux pump. Resistance to aminoglycosides caused by ribosomal mutations can arise from mutations in the *rrs* gene in the ribosomal 16S rRNA, thus, it blocks the binding of aminoglycosides. Mutations occur in nucleotide A1408G by disrupting the hydrogen bond interaction between 2-deoxystreptamine (2-DOS) aminoglycosides and h44 nucleotide A1408. Methylation of 16S rRNA through RNA *methyltransferases* (RMTase) by methylating nucleotides at site A that is the binding site for aminoglycosides in the ribosomal 16S rRNA using S-Adenyosyl-L-Methionine (SAM) as a co-substrate. Enzyme modification is by mimicking the aminoglycosides rRNA target, and it can also pair with

the aminoglycosides in the replacement of the target molecule and deactivate it.[77,80,81] AAC (6′) - Ib is a clinically important enzyme found in gram-negative pathogens, that induces resistance the aminoglycoside.[79,82] The AAC (6') gene induces the Bi-Bi reaction mechanism in which acetyl-CoA binds to the enzyme first, followed by aminoglycosides. A Bi-Bi reaction is where an enzyme catalyses more than one substrate.[77] The efflux pump is a defence against bacteria to prevent the accumulation of antibiotic molecules on the target by reducing the absorption of the molecules or increasing their removal, or simultaneously. The main aminoglycosides efflux pump in Gram-negative bacteria, namely AcrAD, is a multidrug transporter and a member of the efflux pump family, namely the Resistance Nodulation Division (RND).[47,76]

Resistance to the use of aminoglycosides has not been widely found.[83] Parenteral administration of gentamicin together with ampicillin is given to children aged 2-59 months as the main choice in severe pneumonia.[84] Several literature source explained the selection of initial dose for patients with nosocomial pneumonia caused by gram-negative bacteria often results in a less than optimal Cmax/MIC ratio. The optimal concentration of aminoglycosides in serum is best achieved by administering a loading dose of aminoglycosides followed by an initial dose for individualized pharmacokinetic monitoring. A review from Tamma *et.al* 2012 reported that the combination of aminoglycosides with beta-lactam also works together for the treatment of gram-negative bacteria.[49] In cases of severe infection due to pathogenic bacteria that cause pneumonia, administration of short-term therapy and high-dose extended-interval aminoglycosides can improve the healing by considering the side effects of aminoglycoside antibiotics such as nephrotoxicity.[78]

CONCLUSION:

19 literature have been reviewed. The author is found that macrolides, quinolones, carbapenems and aminoglycosides antibiotics are resistant, especially to Gram-negative bacteria that cause pneumonia. Resistance comes from various factors such as gene mutations in macrolides such as (A2063G in 23S rRNA), quinolones such as (gyrA and ParC), aminoglycosides such as (AAC (6′) - Ib in the 16S rRNA gene), and carbapenems through inactivation by β- lactamase enzymes. To increase the effectiveness of antibiotics, combination regimens and increased doses are recommended. Based on studies that have been reviewed, it is necessary to carry out antibiotic sensitivity checks before use.

CONFLICT OF INTEREST:

The authors have no conflicts of interest regarding this investigation**.**

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