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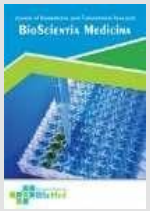

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Antibiotic Management in Bacterial Pneumonia: A Narrative Literature Review

Yusri Herdika[1*], Rohani Lasmaria[1]

[1]Department of Pulmonology and Respirology Medicine, Faculty of Medicine, Universitas Riau, Pekanbaru, Indonesia

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***Corresponding author:**
Yusri Herdika

E-mail address:
Yusriherdika60@gmail.com

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A B S T R A C T

Pneumonia is an acute inflammation of the lung parenchyma caused by various types of microorganisms, such as bacteria, viruses, fungi, and parasites. The use of antibiotics is often faced with many types and inappropriate doses, and using antibiotics for too long can increase the risk of bacteria multidrug resistance (MDR). Therefore, the choice and dosage of antibiotics must be appropriate to reduce the rate of bacterial resistance. The increasing incidence of bacterial resistance is an indicator of failure in treating pneumonia because, apart from clinical improvement, optimal eradication of bacteria should also be the goal in every antibiotic administration. The aim of this literature review is to explain the basis for administering and selecting empiric antibiotics for pneumonia infections as well as appropriate antibiotic management and adequate especially in bacterial pneumonia, to provide a better prognosis.

1. Introduction

Pneumonia was first introduced by Hippocrates around 370-460 BC. Research on pneumonia has been going on for a long time and began to be intensively carried out in the 1800s. In 1819, a clinician named Renè Laennec described pneumonia based on clinical and pathological appearances. Pneumonia is an acute inflammation of the lung parenchyma caused by various microorganisms such as bacteria, viruses, fungi, and parasites. The classification of pneumonia based on clinical and epidemiology is divided into community-based pneumonia or community-acquired pneumonia (CAP), hospital-acquired pneumonia (HAP), and ventilator-associated pneumonia (VAP).[1,2] According to data from the World Health Organization (WHO), pneumonia is in the top five diseases with the highest death rate in the world. According to research data in 2018, the Ministry of Health of the Republic of Indonesia recorded that the number of pneumonia cases based on health worker diagnosis and symptoms reached 4.5% of the 100,000 population. Research data in 2012 the number of inpatient CAP patients in Indonesian hospitals: 4.7% in Persahabatan General Hospital, 25.5% in Dr. Soetomo General Hospital, 11.7% in Dr. Moewardi General Hospital, 16.6% in Dr. M. Djamil General Hospital and 7.2% at Adam Malik Central General Hospital. According to data from Arifin Achmad General Hospital Pekanbaru, the number of CAP cases in 2021 is 398. There were 134 HAP patients and 38 VAP patients out of the total cases of lung disease treated stay.[2,3-5]

The main therapy for bacterial pneumonia is antibiotics, which are supportive and anti-inflammatory, and in this literature review, the author will specifically discuss antibiotic management in

bacterial pneumonia. The use of antibiotics is often faced with many types and inappropriate doses, and using antibiotics for too long can increase the risk of bacteria multidrug resistance (MDR). The increasing incidence of bacterial resistance should be considered as an indicator of failure in treating infections because apart from clinical improvement, optimal eradication of bacteria is also the goal in every administration of antibiotics.[2,3,6-.8] Several circumstances can hinder the provision of appropriate and rational antibiotic therapy, such as firstly, delays in diagnosing and identifying the risk of bacteria causing MDR pneumonia, and secondly, physiological disorders in critical illness that change the pharmacokinetics and pharmacodynamics of antibiotics. The aim of this literature review is to explain the basis for administering and selecting empiric antibiotics for pneumonia infections as well as appropriate and adequate antibiotic management, especially for bacterial pneumonia, to provide a better prognosis.[2,3]

Antibiotics for pneumonia

Antibiotics are often used in many types and in inappropriate doses, and too long of use can increase the risk of bacterial multidrug resistance (MDR). The increasing incidence of bacterial resistance should be considered as an indicator of failure in treating infections. Antibiotics should be given properly, and ideally, the antibiotics given do not cause hypersensitive reactions and have good solubility so that penetration into the tissue can be optimal, do not damage the normal microflora in the body, are bactericidal and not bacteriostatic, do not cause side effects when used for a long period of time, Bactericidal levels in the body are reached quickly and persist for a long time. Antibiotics work by inhibiting the growth and killing bacteria. Antibiotics that work by killing many species of bacteria include broad-spectrum antibiotics, while antibiotics that kill only a few species of bacteria are called narrow-spectrum antibiotics. Mechanism of action of antibiotics to bacteria in cells, namely the first antibiotic that inhibits the synthesis of peptidoglycan in the cell walls of bacteria such as the β-lactam (penicillins, cephalosporins, and carbapenems) and the glycopeptide group (vancomycin, bacitracin). Both antibiotics inhibit the synthesis of lipoprotein molecules in the cell membrane, thereby increasing permeability, and the substances inside the cell can leak out, for example, polymyxin and daptomycin. The three inhibitors of bacterial protein synthesis bother protein synthesis without disturbing normal cells and inhibiting the protein synthesis stage. The bacteriostatic effect works by affecting the function of the 30S or 50S ribosomal subunit, causing reversible inhibition of protein synthesis. Bactericidal effect by forming bonds with the 30S ribosomal subunit and changing protein synthesis, which will ultimately result in cell death, for example, aminoglycosides, amikacin, gentamicin, macrolides, and azithromycin. The four antibiotics that affect nucleic acid metabolism by inhibiting RNA polymerization and inhibiting topoisomerase are quinolones and Rifampicin. Fifth, changing the permeability of the cell membrane by eliminating membrane permeability causes the cell to lyse, for example, nystatin and amphotericin. Sixth, in concentration-dependent killing, antibiotics will produce maximum killing power if antibiotic levels are high or in large doses, for example, aminoglycosides and fluoroquinolones. Seventh, it inhibits the synthesis of folic acid by making bacteria unable to absorb folic acid but must make folic acid from benzoic amino acids (PABA), for example, group sulfonamides, trimethoprim.[9,10]

Cephalosporins

First-generation cephalosporins include cefazolin, cefadroxil, cephalexin, cephalothin, cefapirin, and cefradin. These drugs are very active against gram-positive cocci, for example, *pneumonia, streptococci,* and *staphylococcus*. Cephalosporins are not active against methicillin-resistant strains of staphylococci; however, new compounds have been developed that have activity against the methicillin-resistant strain of *E. coli, Klebsiella pneumoniae*, but activity against *Enterobacter sp,* and *Acinetobacter sp* is low. Second-

generation cephalosporins are cefachlor, cefamandol, cefonisid, cefuroxime, cefprozil, lorakarbef, and ceforanid and cefamycin, which are structurally related to cefoxitin, cefmetazol, and cefotetan, which has activity against anaerobes. This is a heterogeneous group with marked individual differences in activity, pharmacokinetics, and toxicity. In general, these drugs are active against organisms inhibited by first-generation drugs, but in addition, they are also active against gram-negative organisms. Third-generation cephalosporins include cefoperazone, cefotaxime, ceftazidime, ceftizoxime, ceftriaxone, cefixime, cefpodoxime proxetyl, cefdinir, cefditoren pivoxil, ceftibuten, and moxalactam. Generational cephalosporins have a wider range of gram-negative bacteria, and some are able to penetrate the blood-brain barrier. Ceftriaxone and cefotaxime are the most active cephalosporins against nonpenicillin-susceptible pneumococci and are recommended as empiric therapy for serious infections that may be caused by. Third-generation cephalosporins are active against intravenous infusion of 1 gram of parenteral cephalosporin, which produces serum levels of 60-140 mcg/mL. The half-life of this drug and the dosing interval vary greatly. Ceftriaxone (half-life 7-8 hours) can be injected once every 24 hours at a dose of 15-50 mg/kg/day. Cefepime is an example of a fourth-generation cephalosporin. These drugs are more resistant to hydrolysis by chromosomal βlactamases (e.g., those produced by Enterobacter). However, like third-generation compounds, this drug is hydrolyzed by broad-spectrum β-lactamases.[11,12]

Empirical antibiotic therapy in pneumonia

Management of pneumonia cases is through rapid diagnosis and immediate initiation of appropriate antibiotics. Empiric antibiotic administration is defined as administering antibiotics before the causative bacteria is known based on the results of bacterial patterns and antibiotic sensitivity at the local hospital. Rational, empirical administration of antibiotics is the selection of antibiotics according to the bacterial pattern and antibiotic sensitivity Antibiogram, location of the infection, dose, and appropriate route of administration as early as possible. The aim of empiric antibiotic therapy is to reduce mortality and treatment costs and is indicated for infections that will worsen the clinical condition or be life-threatening. Empiric antibiotic administration must consider each individual and is classified into two categories, namely, emergency and urgency.[13,14] We can see the indications and time to start empiric antibiotic therapy in Table 1.

Table 1. Indications and timing of starting empiric antibiotic therapy.

Category	Time	Clinical
Emergency	One hour	Severe sepsis - septic shock Infection accompanied by: Meningeal stimulation Neutropenia Splenectomies
Urgency	> One hour	Suspicions of severe infection, general condition, and stable hemodynamics still require diagnostic confirmation, for example, suspicion of ventilator-associated pneumonia pending radiological results

CAP management

Antibiotics for outpatient CAP patients should be given as soon as possible. For CAP patients coming through emergency departments (ED), antibiotics must be given within 8 hours of entering the ER. If given less than 4 hours, it can reduce the death rate, and if the patient cannot be stabilized and there is respiratory distress, then the patient is treated in the

intensive care unit. Patients receiving antibiotics should be clinically evaluated within the first 72 hours to assess the effectiveness and possibility of changing the antibiotic. When administering antibiotics, epidemiological data on bacteria and local antibiotic sensitivity must be taken into account. If there is clinical improvement, the empiric antibiotic therapy given is continued, but if there is clinical worsening, the antibiotic must be changed according to the culture results. CAP treatment guidelines recommend doing stratification of patients in the risk group, selecting appropriate empiric antibiotic therapy based on germ pattern maps, pharmacokinetics and pharmacodynamics of drugs as well as the presence or absence of drug allergies, history of previous antibiotic use, drug side effects, local pathogens, and drug prices. The aim of giving antibiotics is to reduce and eradicate germs, reduce morbidity and mortality, and minimize bacterial resistance.[15,16]

The guideline for empirical antibiotic therapy for outpatient CAP patients based on the PDPI is that the history must clearly ask whether the patient has previously had a history of using antibiotics in the previous three months. If there is no previous history of antibiotics, the choice of antibiotic therapy used is group βeta lactams such as oral 3rd generation cephalosporins, namely cefixime with a dosage of 400 mg per day divided into two doses per 12 hours for 5 - 7 days if creatinine clearance is normal and the dose is reduced by 50-70% if there is increased creatinine clearance. In Table 2, we can see empiric antibiotic therapy in CAP.

Management of HAP and VAP

Initial clinical treatment of HAP considers the benefits of administering empiric antibiotics to reduce mortality rates by paying attention to the long use of broad-spectrum antibiotics and the emergence of antimicrobial resistance. Every hospital should create and disseminate an antibiogram. Antibiograms are made periodically based on local microbial patterns at certain time periods. Initial antibiotic treatment is empiric, with a choice of antibiotics capable of covering 90% of the possible causative pathogens, taking into account the antibiogram pattern. Empiric antibiotic treatment for HAP recommended based on PDPI and IDSA 2016 modifications with MRSA risk factors or without MRSA risk can be seen in Table 3, and empirical therapy for VAP can be seen in Table 4.[17,18]

Definitive therapy

Definitive therapy is the administration of antibiotics based on the results of microbiological culture and the results of bacterial sensitivity tests to antibiotics that correspond to the pathogenic bacteria found. Antibiotic therapy caused by *Pseudomonas aeruginosa* can be given monotherapy in conditions without septic shock, without risk of death, and with known antibiotic sensitivity results. Combination antibiotics are given if accompanied by septic shock. The risk of death and the results of the sensitivity test are known. Selection of therapy after obtained culture results should be given therapy appropriate to the type of microorganism being examined according to the antibiogram.[19]

Antibiotic de-escalation

De-escalation is one effort to prevent the growth of resistant strains of bacteria and reduce bacterial exposure to antibiotics. If the clinical appearance, laboratory improvement, and changes to narrow spectrum antibiotics based on antibiotic sensitivity results can be seen from the antibiogram chart. The duration of administration of narrow-spectrum antibiotics is expected to be 7-10 days, and if the clinical response to antibiotic therapy does not improve, then antibiotic therapy is given for 15 days. Antibiotics can be stopped if clinical improvement occurs and laboratory test results also improve.[18,19]

Table 2. Guidelines for empiric antibiotic therapy in CAP.

Without comorbidities or risk factors for antibiotic resistance on an outpatient basis, choose one.
Amoxicillin 3 x 1000mg OR
Doxycycline 2 x 100mg OR
Macrolides: Azithromycin 1 x 500mg (first day) followed by 1 x 250mg/day **OR** Clarithromycin 2 x 500mg or 1 x 1000mg) → only in areas with pneumococcal resistance to macrolides <25%.
With comorbid or outpatient risk factors for antibiotic resistance, choose one. (chronic diseases of the heart, pulmonary, liver, or renal, diabetes mellitus, history of alcohol, malignancy, or asplenia), choose one:
a. Combination Therapy
Amoxicillin / Clavulanate 3 x 500mg / 125mg, 2 x 875mg / 125mg, 2 x 2000mg / 125mg OR Cephalosporins (Sefpodoksim 2 x 200mg OR Sefuroxim 2 x 500mg).
And
Macrolide (Azithromycin 1 x 500mg the first day followed by 1 x 250mg OR Clarithromycin 2 x 500mg or 1 x 1000mg) OR Doxycycline 2 x 100mg.
b. Monotherapy
Fluoroquinolone respiration (Levofloxacin 1 x 750mg OR Moxifloxacin 1x 400mg) OR Gemifloxacin 1 x 320mg).
Hospitalization, without risk of MRSA or *P. aeruginosa,* choose one.
a. Not severe CAP. Choose one:
Combination therapy
B-lactam (Ampicillin-sulbactam 1.5 - 3gr every 6 hours, OR Sefotaxime 1-2gr every 8 hours, OR Seftriaxone 1 x 1-2gr, OR Seftaroline 600mg every 12 hours).
And
Macrolides (Azithromycin 1 x 500mg, OR Clarithromycin 2 x 500mg)
Monotherapy
Fluoroquinolone respiration (levofloxacin 1 x 750mg OR Moxifloxacin 1 x 400mg)
Contraindicated with macrolides or fluoroquinolones of respiration
B-lactam (Ampicillin-sulbactam 1.5-3gr every 6 hours, OR Sefotaxime 1-2gr every 8 hours, OR Seftriaxone 1 x 1-2gr, OR Seftaroline 600mg every 12 hours).
And
Doxycycline 2 x 100mg.
b. Severe CAP, choose one:
-B-lactam (Ampicillin-sulbactam 1.5-3gr/6 hr, OR Sefotaxime 1–2gr/8 hr, OR Seftriaxone 1 x 1-2gr, OR Seftaroline 600mg/12hr).
And
Macrolides (Azithromycin 1 x 500mg, OR Clarithromycin 2 x 500mg)
-B-lactam (Ampicillin-sulbactam 1.5-3gr/6 hours, OR Sephotaxime 1-2gr every 8 hours, OR Seftriaxone 1 x 1-2gr, OR Seftaroline 600mg/12 hours)
And
Fluoroquinolone respiration (levofloxacin 1 x 750mg OR Moxifloxacin 1x400mg).
Hospitalization, with risk factors MRSA or *P. aeruginosa*:
a. Inpatient MRSA empirical therapy.
Vancomycin 15mg/kgBB/12 hours OR Linezolid 600mg/12 hours.
b. Empirical therapy of *P. aeruginosa*
Piperacillin-tazobactam 4.5gr/6 hours OR Cefepim 2gr/8 hours, OR Ceftazidim 2gr/8 hours, OR Aztreonam 2gr/8 hours, OR Meropenem 1gr/8 hours, OR Imipenem 500mg/6 hours.

Table 3. Empirical therapy in HAP without MRSA risk factors.

Without high risk of mortality and has no risk factors for MRSA
Choose one of the drugs below:
Cefepime 2gr IV per 8 hours
Piperacillin for tazobactam 4.5 gr/6 hours
Levofloksasin 750 mg IV per 24 hours
Imipenem 500 mg IV per 6 hours
Meropenem 1 gr IV per 6 hours
Without the risk of mortality but have risk factors for MRSA, choose one of the drugs below + MRSA drug
Cefepime 2 gr IV per 8 hours
Levofloxacin 750 mg IV per 24 hours Or ciprofloxacin 400 mg IV per 8 hours
Meropenem 1gr IV per 8 hours
Aztreonam 2gr IV per 8 hours
Piperacillin tazobactam 4.5gr IV per 6 hours
Plus
Vancomycin 15mg/kg IV every 8-12 hours with a target of 15 -20mg/ml with levels loading *dose* 25-30mg /kg x 1 for severe disease
Or
Linezolid 600 mg IV per 12 hours
Risk of mortality or history of IV antibiotic use in the last 90 days. Choose two of the following by avoiding beta-lactams + MRSA drugs
Piperacillin tazobactam 4.5g per 6 hours
Cefepime 2gr IV every 8 hours Or
Levofloxacin 750mg IV every 24 hours or ciprofloxacin 400mg IV every 8 hours
Imipenem 500mg IV every 6 hours or Meropenem 1gr IV every 8 hours
Aminoglycosides ➔
Amikasin 15-20mg per kg IV per 24 hours
Gentamicin 5-7mg per kg IV per 24 hours
Tobramisin 5-7mg per kg IV per 24 hours
And
Vancomycin 15mg per kg IV every 8-12 hours
Linezolid 600mg IV per 12 hours
If you don't use an antibiotic that covers MRSA, then use an antibiotic that covers MSSA. The options are:
Piperasilin tazobaktam, cefepim, levofloksasin, imipenem, meropenem
Oxacillin, nafcillin, and cefazolin are used if MSSA is proven, but generally not used as an empiric regimen for HAP

Table 4. Empirical therapy for VAP.

Gram-positive with MRSA
Vancomycin 15 \ mg/kg IV per 8-12 hours with a target of 15 -20 mg/ml with levels loading dose 25-30mg /kg x 1 for severe disease
Or
Linezolid 600mg IV per 12 hours
Gram negative with pseudomonas beta-lactam
Cefepime 2gr IV per 8 hours
Meropenem 1gr IV per 8 hours
Aztreonam 2gr IV per 8 hours
Piperacillin tazobactam 4.5gr IV per 6 hours
Gram negative with non-beta-lactam pseudomonas
Levofloxacin 750mg IV every 24 hours or ciprofloxacin 400 mg IV every 8 hours
Aminoglycosides:
Amikasin 15-20mg per kg IV per 24 hours
Gentamicin 5-7mg per kg IV per 24 hours
Tobramisin 5-7mg per kg IV per 24 hours

Table 5. Selection of definitive antibiotics in HAP.

Types of microbes	**Types of antibiotics**	**Dose**
MRSA	Vancomycin Linezolid	15mg/kgBW/12 hours 600mg2x/day in 30 minutes
MSSA	Amoxil	3x2g IV
	Seftriakhan	1gr IV/day
	Levofloxacin	750 mg IV per day over 30 minutes
P.aeruginosa	Cefepime	2g IV 2-3x/ day
	Ceftazidime	2g IV 3x / day
	Levofloxacin	750mg IV per day in 30 minutes
	Ciprofloxacin	400mg IV per day
	Meropenem	1gr IV 3x/ day
	Immensely	0,5 –1gr 4x/ day
Klebsiella pneumonia	Amoxicillin clavulanate	3x2 gr
	Seftriakhan	1gr IV/day
	Cefotaxime	3x2gr
	Levofloxacin	750mg IV per day
Acinetobacter	Ampicillin sulbactam	3x3gr
	Meropenem	1gr IV 3x/ day
	Immensely	0,5-1gr IV 4x/ day

Switching therapy

Switching therapy is a switch from parenteral antibiotics to oral antibiotics during the interval of initial clinical improvement whose effectiveness is comparable to or equal to the antibiotics previously used. According to PDPI, the criteria for changing from injection to oral medication in CAP are stable hemodynamics, improved clinical symptoms, being

able to take medication orally, and normal gastrointestinal function. The ideal antibiotic selection for replacement therapy is an oral antibiotic spectrum that is identical to intravenous and an administration schedule of once or twice a day so that it will increase patient compliance. These changes can be administered sequentially (same drug, same potency), switch over (different drugs, same potency) and step down (same or different drug, lower potency). Sequential examples are Levofloxacin and Moxifloxacin. Examples switch over is ceftazidime IV (intravenous) to oral Ciprofloxacin, while examples step down are Amoxicillin, Cefuroxime, IV Cefotaxime to oral Cefixime. Injectable medication can be given for 2-3 days. The safest is 3 days then on the 4th day, it is changed to oral medication, and the patient can seek outpatient treatment. CAP patients treated in the intravenous administration room can be switched to oral therapy after 3 days, and patients in the intensive care unit can be given oral therapy after 7 days. We can see the choice of antibiotics for replacement therapy in CAP from Table 6.[20]

Table 6. Selection of antibiotics for replacement therapy in CAP.

Drug class	Recommended oral antibiotics	Other antibiotic options
Levofloxacin	Levofloxacin	Flourokuinolon
Ampicillin	Ampicillin	βlactam+macroles
Cefuroksim	Cefuroksim	Cefaklor,cefadroksil, flourokuinolon
Ceftriaxone, cefotaxime	Cefuroksim	Cefixime, cefpodoxime,
Ceftazidime, imipenem, piperacillin/tazobactam	Cefuroksim	Flourokuinolon
Azithromycin	Azithromycin	Fluoroquinolone doxycycline
Doxycycline	Doxycycline	Flourokuinolon
Clindamycin	Clindamycin	Metronidazole, + β-lactam, flourokuinolon

Assessment of the effectiveness of pneumonia therapy

CRP examination can be repeated in CAP patients on the third or fourth day of antibiotic therapy. An increase in CRP identifies the patient's risk of failed therapy and/or increased risk of complications. A CRP value > 10 mg/dl on the fourth day of therapy will increase the risk of complications. Patients with CRP levels < 3 mg/dl on the third day of therapy will have a reduced risk of complications. In addition, patients whose CRP levels do not decrease by 50% on the fourth day of therapy have a high mortality rate within 30 days, an increased risk of mechanical ventilation and use of vasopressor drugs, and a high risk of pyothorax as a complication of CAP. PCT examination is a marker of etiology and a better prognosis for pneumonia compared to other markers such as CRP and erythrocyte sedimentation rate (ESR). A decrease in the PCT value indicates improvement in infection, and an increase in the PCT value of more than 2mg/ml indicates a poor prognosis. PCT can help clinicians predict classic bacteria and help determine empiric antibiotics. Deterioration of the patient's condition and non-response to initial therapy should warrant aggressive evaluation to look for possible differential diagnoses. The prognosis worsens if complications of pneumonia occur, such as lung abscesses and empyema.[21]

2. Conclusion

Pneumonia is an acute inflammation of the lung parenchyma caused by various types of

microorganisms, such as bacteria, viruses, fungi, and parasites. The main therapy for bacterial pneumonia is antibiotics, support, and anti-inflammatories. Using the wrong type of antibiotic and antibiotic dose, as well as using antibiotics for too long, can increase the risk of bacterial multidrug resistance (MDR). The increasing incidence of bacterial resistance should be an indicator of failure in treating infections because, apart from clinical improvement, optimal eradication of bacteria is also the goal in every antibiotic administration.

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