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Spotlight on Antibiotics Treatment for the Pneumonia: A Review

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Abstract

Pneumonia is a major infectious disease worldwide, with high morbidity, mortality and healthcare costs. Community-acquired pneumonia (CAP) remains the leading cause of death from infectious diseases worldwide, with the greatest impact of community-acquired pneumonia on morbidity and mortality. especially in under 5 years old children and the elderly. The World Health Organization (WHO) predicts that by at least 2030, pneumonia will be among the top four causes of death. Pneumonia may present as community-acquired pneumonia (CAP) in critically ill patients. Pneumonia is associated with high long-term mortality, and survivors often have significant costs, including lung function, mental impairment, weakness, and disability. Antibiotics are widely used in ICUs in the world. The most common typical organisms include Streptococcus pneumoniae, Haemophilus influenzae, group A Streptococcus, Moraxella catarrhalis, and other anaerobic and aerobic Gram-negative bacteria. Atypical organisms commonly found in the clinical setting include Mycoplasma, Legionella, and Chlamydia. The ATS/IDSA CAP Guidelines were published in 1996 and contain changes to previous recommendations.

Keywords-Pneumonia, Antibiotics, Empirical therapy, Critical illness, Carbapenem, Combination therapy, Intensive care units.

Introduction

Pneumonia is a major infectious disease worldwide, with high morbidity, mortality, and healthcare costs. (File Jr, et al.,2010; Welte et al., 2012). Data from the 2015 Globally Disease Study showed that lower respiratory tract infections, including pneumonia, were the third leading cause of death after ischemic heart disease and vascular disease brain perfusion. Pneumonia remains the leading cause of death from infectious diseases in worldwide, with the greatest impact of pneumonia on morbidity and mortality concentrated particularly in five year old children and the elderly. there is The World Health Organization (WHO) predicts that by at least 2030, pneumonia will be among the top four causes of death.(Ramos-Rincón et al., 2019).Despite recent advances in antimicrobial therapy, pneumonia remains one of the leading infectious causes of intensive care units (ICU).(Çelikhisar et al., 2021)

Pneumonia may manifest as community-acquired pneumonia (CAP) and Ventilator-associated pneumonia (VAP). Severe pneumonia is associated with high short and long-term mortality, and survivors often have significant outcomes including altered lung function, mental and debility and disability Movement.(Cillóniz et al., 2021)

Pneumonia is a common condition that causes a significant disease burden in the population. Pneumonia is especially dangerous for children under five year old and the elderly, and those with many other conditions that can affect the immune system, such as "diabetes, HIV/AIDS, and organ transplant patients." Antibiotics are the most common treatment for pneumonia.(Tjm & Ggu, 2014)

Community-acquired pneumonia (CAP)

Community-acquired pneumonia is defined by the presence of acute symptoms and signs of lower respiratory tract infection (LRTI) with no other apparent cause requiring pulmonary infiltration. A chest x-ray is done to confirm the diagnosis. The most common signs and symptoms are shortness of breath, cough, fever, and new chest symptoms. In subgroups of patients (e.g., the elderly), clinical manifestations may be less evident (e.g., disturbed consciousness, gastrointestinal symptoms, fever may be absent) and diagnosis is often delayed. Patients with mild pneumonia, alcoholics, and those taking medications such as corticosteroids and anti-inflammatory drugs report longer delays between the onset of symptoms and seeking medical attention. Non-steroidal and antibiotics. Some pathogens often seen in unusual clinical

manifestations, with slowly onset symptoms such as dry cough, absence of fever, and extrapulmonary manifestations.(Prina et al., 2015)

Primary treatment of pneumonia is usually empirical. Many international guidelines recommended empirical treatment based on the hospitals, with specifically recommend for outpatients, inpatients, and patients undergoing critical care**.**(Wongsurakiat & Chitwarakorn, 2019)

Ventilator-associated pneumonia (VAP)

Ventilator-associated pneumonia (VAP) is pneumonia that develops more than 48–72 hours after intubation and is characterized by the presence of new or progressive infiltrates and clinical signs and symptoms. Systemic infections (fever, low white blood cell count), changes in sputum characteristics, and detection of pathogens. VAP accounts for about half of hospital-acquired pneumonia cases. VAP is estimated to occur in 9-27% of all ventilated patients and is at greatest risk early in hospital admission. This is his second most common nosocomial infection in the intensive care unit and most common in patients on ventilators. VAP risk was highest during the first 5 days on mechanical ventilation (3%), with a median time from intubation to VAP onset of 3 days.(Kalanuria et al., 2014)

Ventilator-associated pneumonia (VAP) is commonest infections occurring in intensive care units. The reported incidence varies widely from 5 to 40 depending on setting and diagnostic criteria. VAP is related to duration of ventilator use and duration of ICU stay.(Papazian et al., 2020)

Antibiotics are widely used in ICUs worldwide.(Versporten et al., 2018). Up to 70% of critical care patients receive empiric or definitive antibiotic therapy now a day. (Timsit et al., 2019)The burden of infection caused by broad-spectrum beta-lactamase-producing Enterobacteriaceae (ESBLE) and multidrug-resistant Pseudomonas aeruginosa is steadily increasing, carbapenem-resistant Acinetobacter baumannii and carbapenemase-producing Enterobacteriaceae (CRE) are spreading globally, while methicillin-resistant Staphylococcus aureus (MRSA) and a large geographic area of vancomycin-resistant disease are causing major problems(Weiner et al., 2016)., Bonell et al., 2019; Detsis et al., 2017; Djordjevic et al., 2017; Bonomo et al., 2018; Gao et al., 2017; Hu et al., 2016; Lob et al., 2015, 2018; Kollef et al., 2014; Nowak et al., 2017 2016; Rosenthal et al., 2016; ; Rodríguez et al.,)

ATS/IDSA guideline

The ATS/IDSA CAP guidelines were published in 1996. In particular, the guidelines recommend the deletion of the health-associated pneumonia (HAP) category to avoid the overuse of empirical broad-spectrum therapy. The prevalence of resistant pathogens is sufficiently low, even in his severe CAP patients, that the introduction of broad-spectrum treatment for all HAP patients has resulted in overuse of the disease. Patients with HAP, who have a high mortality rate from CAP, often have not only pathogenic risk factors but also clinical features and multiple comorbidities that compromise survival. Drug resistance. In addition, the leading adverse events have also been reported: B. Increase in Clostridium difficile infections associated with overuse of broad-spectrum antibiotics. (Chung et al., 2014)

Pathogenesis of pneumonia

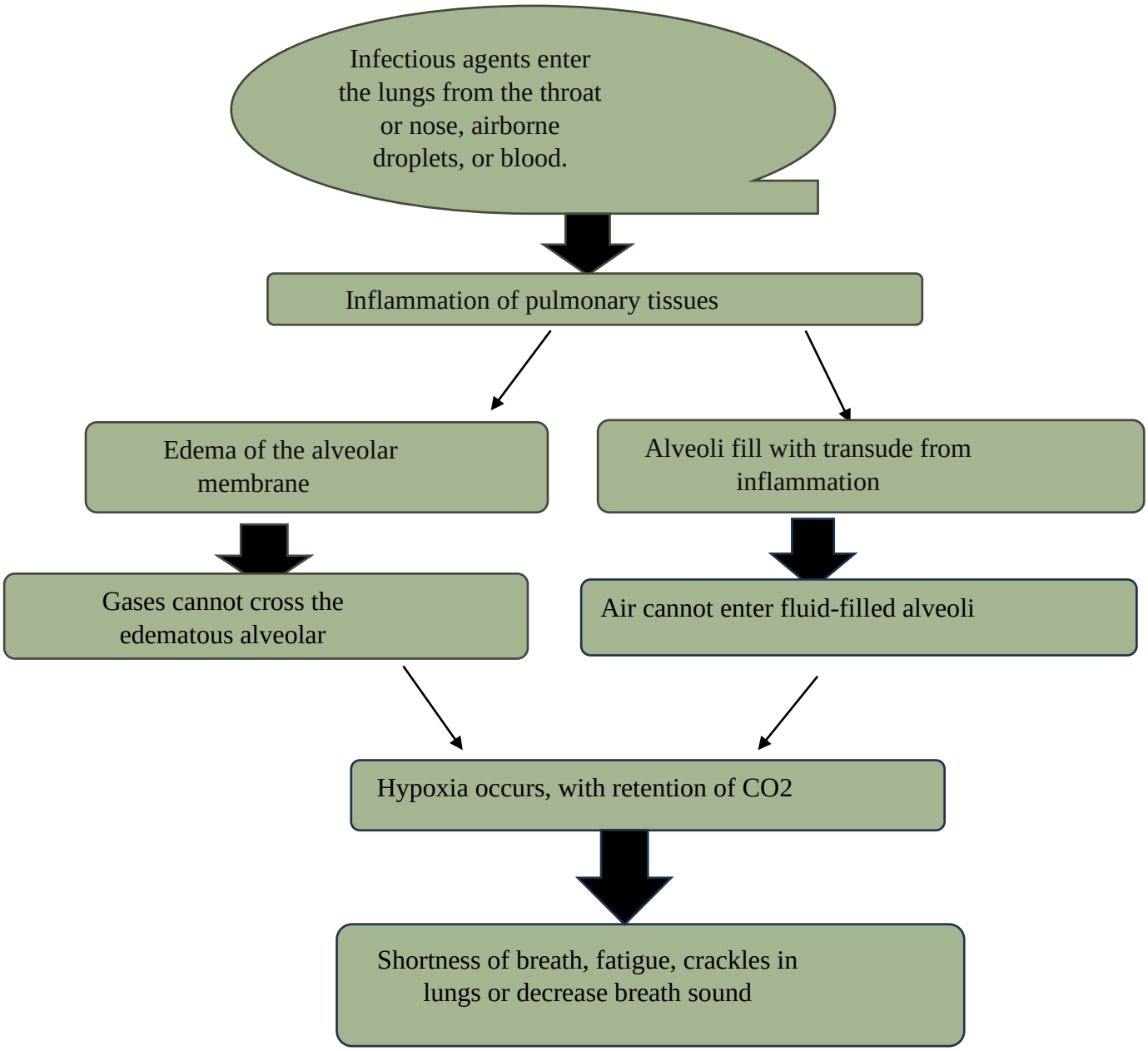

Table 1. : Pathogenesis of pneumonia

Identification of the causative agent of pneumonia is essential for both effective treatment and epidemiological record keeping but is rarely observed in clinical practice. Studies have shown that less than 10% of patients presenting to the emergency room often have pneumonia as their sole cause. (Bartlett et al., 2011)

Bacterial causes

In the current studies under the sub-headings of 'typical' and 'atypical' organisms regarding ease of cultural positivity. The various common typical organisms include Haemophilus influenzae,Streptococcus pneumoniae, Moraxella catarrhalis, Group A Streptococcus, and other aerobic and anaerobic Gram-negative bacteria. Atypical organisms commonly found in clinical settings include Legionella, Mycoplasma, and Chlamydia.

Viral causes

The virus usually colonizes the virus species in her CAP patient's nasopharynx. Whether they are the main cause or contribute to pathogenesis by secondary bacterial causes is still under investigation. However, the most typical viral agents thought to be associated with CAP in the United States include influenza virus, followed by respiratory syncytial virus,and adenovirus, parainfluenza virus.(Jain et al., 2015)

Caused by Fungus

Fungal infections are common in patients predisposed to certain immunodeficiency diseases, such as HIV and organ transplant recipients. What is often overlooked, however, is that certain types of fungi can cause pneumonia in people with healthy immune systems, delaying diagnosis and having unfavorable consequences. (Hage et al., 2012)

Pneumonia is a severe infection that occurs when pathogen virulence defeats the host's defense. With aging, there is a general decline in organ function, which determines not only an individual's risk of pneumonia but also clinical presentation and outcome. In addition to increased clinical complexity and more rapid disease progression, older patients are at increased risk of pneumonia from resistant organisms such as Gram-negative bacilli, making both empirical and definitive treatment difficult. may become. The incidence of pneumonia

increases with age, as does the impact of pneumonia morbidity and mortality.(Henig & Kaye, 2017)

Many studies have elucidated the causative agent of HAP. Gram-negative bacteria such as Pseudomonas aeruginosa, Enterobacter, Acinetobacter, and Gram-negative bacilli are thought to be responsible for 55-85% of HAP cases**.** (Lynch J et al., 2001)

Pathogens and Pneumonia

In most cases of pneumonia, the exact pathogen is unknown. Although many culture-based molecular laboratory tests are now available to help identify pathogens, a recent international study reported a pathogen detection rate of only 36.5% in adults hospitalized with CAP. One of the major limitations of this reported distribution is that LRT samples are often not collected from patients with pneumonia due to the invasive nature of lower respiratory tract sampling. However, viral infection is usually confirmed by PCR performed on more readily available nasopharyngeal or oropharyngeal swabs.

Viral pneumonia

RNA viruses such as influenza and rhinovirus are commonly associated with pneumonia, but parainfluenza virus,respiratory syncytial virus, adenovirus, human meta pneumonia virus, and coronavirus also cause pneumonia. Obesity and metabolic syndrome have been clearly described as an increased risk of serious illness from viral infections such as influenza and SARS-CoV-2. Overall, respiratory viruses is the leading cause of pneumonia, and epidemic and pandemic viruses still have potential to significantly disrupt life around the world.

Bacterial Pneumonia

Bacteria, including both Gram-negative and Gram-positive bacteria, are common causes of PACs and PAHs. The common cause of bacterial pneumonia is infection with Streptococcus pneumoniae. With at least 98 serotypes circulating, vaccination strategies against pneumococci are displacing endemic serotypes in individuals. The World Health Organization has classified the pathogens Staphylococcus aureus, ESKAPE, Enterococcus faecium, Acinetobacter baumannii, Klebsiella pneumonia, Pseudomonas aeruginosa, and Enterobacter is major threats. (Long et al., 2022)

Risk factors for pneumonia

* **Age** - Below 5 years. - Above 65 years.
* **Lifestyle** - chronic smoking - chronic alcoholism - Poor nutritional status
* **Diseases** - Chronic renal disease - Chronic heart disease - Chronic liver disease - Chronic bronchitis/ COPD - Asthma - Metabolic disease - CNS disease - Previous pneumonia - Diabetes
* **Immunocompromised** - asplenia /splenic dysfunction - Primary immunodeficiencies
* **AIDS** * **ARDS**
* **Immunosuppression** - Immunosuppressive therapy - Organ transplantation - Cancer with immunosuppressive treatment
* **Drugs** - Proton pump inhibitors or H2 antagonists - Receiving steroid

Table 2. (ARDS-acute respiratory distress syndrome, **COPD-**Chronic obstructive pulmonary disease**, CNS**- central nervous system**, AIDS-** acquired immunodeficiency syndrome**)**

(Jung et al., 2021; Almirall et al., 2017; Lynch, 2001b; Torres et al., 2013

Novel anti-bacterial drugs for Pneumonia

Initial antibiotic choice in the current scenario

In most patients with severe CAP, initial therapy consists of a combination of beta-lactam and a macrolide or fluoroquinolone. For patients without MRSA or pseudomonas risk factors, beta-lactams can be cefotaxime, ceftriaxone, or ampicillin-sulbactam. Beta-lactams such as piperacillin/tazobactam, cefepime, ceftazidime, imipenem, or meropenem can provide some pathogen coverage in individuals with the risk factors for pseudomonas infection. Aztreonam is an alternative drug for people with beta-lactam allergies. (Lázár et al., 2022)

How to choose a broad-spectrum antibiotic?

In severe CAP, there is evidence that the combination of β-lactams and macrolides significantly improves patient prognosis compared with treatment without macrolides. Clindamycin and linezolid inhibit toxin production and block bacterial protein synthesis. As recommended by the ATS/IDSA guidelines, antibiotic therapy for MRSA should only be used if the patient has risk factors for her MRSA (has previously isolated airways for her MRSA). has been hospitalized for MRSA recently). [within the past 90 days] and parenteral antibiotic use [within the past 90 days], and community-validated risk factors for MRSA). Physicians should also collect a sample for culture and perform a nasal PCR test to determine whether to de-escalate or continue treatment. Empiric treatment options for MRSA include vancomycin 15 mg/kg/12 hours (level-adjusted) or linezolid 600 mg/12 hours. For patients with severe necrotic CAP, antivenom can be added to treatment (which also has antitoxic effects), such as vancomycin with clindamycin or linezolid alone. Linezolid penetrates the lungs better than vancomycin, but doctors give it more often for HAP and VAP than for CAP. (Payne et al., 2021)

Monotherapy of antibiotics in the present scenario-

1. **NEW CEPHALOSPORINS: CEFIDEROCOL**

   Cefiderocol, formerly S-649266, is an injectable cephalosporin with a unique mechanism of action. bacterial cell invasion. Cefiderocol binds to iron and is actively transported into bacterial cells through the outer membrane through bacterial iron. Passive transport and diffusion through porins channels in the periplasmic space. Cefiderocol has demonstrated in vitro activity against Enterobacteriaceae and ESBL-producing CREs (including types A, B, and D), as well as against meropenem resistant to P. aeruginosa, Stenotrophomonas maltophilia, and A. baumannii. The APEKS-cUTI study showed that cefiderocol achieved results not inferior to high results dose of imipenem/cilastatin in hospitalized adults Patients

with urinary tract infections (cUTI) are at risk of infection with Gram-negative bacteria MDR and well-tolerated.(Khajehali & Alizadeh, 2017; Yi et al., 2018.,)

2. NEW OXAZOLIDINONES: TEDIZOLID–

Tedizolid is a new oxazolidinone approved by Food and Drug Administration (FDA) and European Health Agency (EMA) for the treatment acute skin and soft tissue infections. Tedizolid has demonstrated potent activity in vitro against MRSA and vancomycin-resistant enterococci, including some linezolid-resistant strains. Tedizolid has more advantages than linezolid, including reduced risk of gastrointestinal upset side effects, myelotoxicity, and reduced risk of medication–drug interactions with compounds with serotonergic and adrenergic activity due to weak and reversible in vitro monoamine oxidase inhibition. Due to the longer half-life of 10 hours, tedizolid should only be given once Daily. The high oral bioavailability of tedizolid (>90%) Allows an easy transition from intravenous to oral. (Lodise et al., n.d.)

3. NEW AMINOGLYCOSIDES: PLAZOMICIN

Plazomycin is a new-generation semi-synthetic aminoglycoside that inhibits protein synthesis of bacteria and exhibits dose-dependent bactericidal effects. Plazomycin has shown potent activity against Gram-positive bacteria such as MRSA, including aminoglycoside-resistant strains. Plazomycin has been transformed into a commonly used resist aminoglycoside-modifying enzyme present in the CRE. Against Gram-negative bacteria, plazomycin is effective against MDR Enterobacteriaceae, including CRE and pre-existing aminoglycoside-resistant isolates. Compared to its activity against Enterobacteriaceae, plazomycin has less activity against non-fermenting Gram-negative bacteria. Against MDR. The MIC of Pseudomonas aeruginosa plazomycin is similar to the MIC of other aminoglycosides. (Wright et al., n.d.)

4. NEW TETRACYCLINES: ERAVACYCLINE

Eravacycline is an experimental, intravenous, and oral synthetic fluorocycline promising, and structurally similar to tigecycline. Like everything else tetracycline, eravacycline inhibits bacterial protein synthesized and demonstrated broad-spectrum antibacterial activity against Gram-positive, Gram-negative, and anaerobic bacteria except P. aeruginosa, which showed greater activity than tigecycline. Some studies in animal models, including rat lung infection, demonstrated in vivo efficacy of eravacycline. Eravacycline may provide an alternative to Patients with VAP caused by Gram-negative bacteria MDR bacteria,

including MDR Acinetobacter. Furthermore, high oral bioavailability (>90%) allowed the switch from intravenous to oral form. (Solomkin et al., n.d.)

Combination therapy of antibiotics in present scenario-

1. Ceftazidime avibactam (CEF/AVI)- is a combination of third-generation cephalosporin and beta-lactamase inhibitors. However, it has no activity against metallo-β-lactamase-like carbapenemases and Acinetobacter oxo. Ceftazidime avibactam have been approved by the Food and Drug Administration (FDA) for use in HAP/VAP.
2. Ceftolozane tazobactam (CEF/TAZ)- and meropenem (1 g every 8 hours infusion). In study, this two agents were similarly effective and well tolerated in ventilated patients with hospital-acquired Gram-negative pneumonia. However, CEF/TAZ has a mortality advantage in his PAH patients on mechanical ventilation and in patients with current stages of nosocomial pneumonia who had failed previous antibiotic therapy. This new antibiotic has FDA and EMA approval for the treatment of HAP.
3. Meropenem-vaborbactam- is a combination drug containing an available beta-lactam antibiotic (meropenem) and a non-beta-lactamase cyclic boronate inhibitor (tazobactam), including bacteria with extended beta-lactamases. Active against Gram-negative pathogens. Spectrum and carbapenemase K pneumonia are effective. However, it was inactive against oxacillinase and Metallo-β-lactamase producing strains. Meropenem vaborbactam is not approved for VAP, but studies in mechanically ventilated patients with resistant Enterobacteriaceae have demonstrated clinical recovery effects compared with the best available therapy (usually colistin). was demonstrated. Carbapenem.
4. Imipenem-sulbactam- It is a combination drug containing an existing (imipenem-cilastatin) and (sulbactam), active against Gram-negative pathogens. There is broad-spectrum β-lactamase and carbapenemase K pneumoniae. However, it was inactive against Metallo-β-lactamase and oxacillinase-producing strains.(Bassetti et al., 2018)

Conclusion

Most studies show that following IDSA/ATS recommendations for shorter antibiotic therapy in hospitalized VAP patients is safe and reduces treatment duration. Microbiological data should be used to customize antibiotic treatment beyond just diagnosis. The pitfalls of empiric antibiotic use in suspected VAP include the potential for overuse, resistance, side effects, and toxicity. The main goal of VAP management is

timely and appropriate antibiotic administration, followed by de-escalation based on culture results and clinical response. HAP is a critical issue in healthcare, causing extended hospital stays, increased costs, and higher morbidity and mortality rates. Its prevalence continues due to the rise of antibiotic-resistant opportunistic pathogens.

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