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Clinical Effectiveness of Beta-Lactam and Macrolide Antibiotics in the Treatment of Pediatric Pneumonia

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ABSTRACT
Pneumonia is an acute lower respiratory infection involving lung parenchyma. Pneumonia is a leading cause of morbidity and mortality in children younger than the age of 5 years. Pneumonia is singly responsible for almost one-fifth of total mortality in vulnerable age groups.Pneumonia kills more children than any other infectious disease, claiming the lives of over 700,000 children under five every year, or around 2,000 every day. This includes over 200,000 newborns. Almost all of these deaths are preventable. Globally, there are over 1,400 cases of pneumonia per 100,000 children, or 1 case per 71 children every year, with the greatest incidence occurring in South Asia [2,500 cases per 100,000 children] and West and Central Africa [1,620 cases per 100,000 children].Pneumonia is transmitted via aspiration of airborne pathogens but may also result from the aspiration. Pneumonia has numerous potential etiologies, the most common of which is infectious, and its classified according to the age group of pediatrics. Pathogen commonly affects the pediatric population and often differ from those seen in adults. Diagnosis is based on history and clinical presentation.The CURB-65 criteria are used for determining the severity of the infection and it is also used for the need for hospitalization. Management involves supportive care and empiric antibiotic treatment is based on the etiologic agent. Oral antibiotics may be used in mild to moderate infections. Intravenous antibiotics are required in severe infections.

KEYWORDS: PNEUMONIA, CLASSIFICATION, BETA-LACTAM, MACROLIDES.

I. INTRODUCTION

The word "pneumonia" originates from the ancient Greek word "pneumon" which means "lung," so the word "pneumonia" becomes "lung disease." Pneumonia is a lower respiratory tract infection characterized by inflammation of the lungs' alveolar space or interstitial tissue. Lower respiratory tract infection can be considered as an infection occurring at an anatomical level below the vocal cords, which would include the clinical syndromes of bronchitis, bronchiolitis, and pneumonia and its complications [1] Pneumonia is a widespread and common infectious lung disease that causes inflammation, which can lead to reduced oxygenation, shortness of breath, and death. [2] Pneumonia is defined as a lower respiratory tract infection [LRTI] typically associated with fever, respiratory symptoms, and evidence of parenchymal involvement by either physical examination or the presence of infiltrates on chest radiography. Pathologically, it represents an inflammatory process of the lungs, including airways, alveoli, connective tissue, visceral pleura, and vascular structures. Radiologically, pneumonia is defined as an infiltrate on a chest radiograph in a child with symptoms of an acute respiratory illness.[3]

CLASSIFICATION OF PNEUMONIA:

Pneumonia can be classified based on location, clinical features, anatomical involvement pattern, etiology, and the patient's immune status. In pediatricpatients, pneumonia may be classified according to their age such as newborn pneumonia, and pneumonia in children above the age of [5].

A. BY LOCATION ACQUIRED:

1. Community-acquired pneumonia:

CAP refers to acute pulmonary infection in a previously healthy individual who has acquired it from the community/outside of a healthcare establishment [4]

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2. Hospital-acquired pneumonia:
It's also known as nosocomial pneumonia, which develops > 48 hours or longer than after hospitalization of a non-intubated patient [5].
3. Ventilator-associated pneumonia:
A type of hospital-acquired pneumonia as a result of mechanical ventilation breathing machines.These types of infectionsare mostly acquitted in patients admitted to intensive care units [6].
4. Healthcare-associated pneumonia:
HCAP was acquired from healthcare facilities such as nursing homes,dialysis centers, hospitals, and outpatient clinics.

B.BY CLINICAL FEATURES:

Typical pneumonia: Pneumonia mostly presents with the classical symptoms,abrupt onset, and manifests as lobar pneumonia or bronchopneumonia. Typical pneumonia is caused by streptococcus pneumonia and Haemophilus influenzas.aureus, Group a streptococcus, Moraxella catarrhalis, anaerobes, and aerobic gram-negativebacteria [7].

Atypical Pneumonia: Pneumonia usually presents with less severeclassical symptoms,more insidious onset, and manifests as interstitial pneumonia. Atypical pneumonia is mostly caused by Legionella's, mycoplasma pneumonia, Chlamydia pneumonia, and C. psittaci [8].

C.BY ETIOLOGY:

Pneumonia pathogens are classified according to pediatricage [9],

VIRUSES:

In children under 5 years, lower respiratory infections [50%] are caused by viruses. The most common causes of viruses include Respiratory syncytial virus [RSV],influenza virus,adenovirus, metapneumovirus,parainfluenza virus, enterovirus, coronavirus, and rhinovirus. [10]

D. PNEUMONIA IN NEONATES [4 WEEKS OLD]:

1. Streptococcus agalactiae, also commonly called Group b streptococci, is a gram-positive bacterium that normally colonizes the vagina.It can be inhaled during the delivery placing the neonate at risk for meningitis,sepsis, and pneumonia.So, pregnant women should be screened for the presence of organisms in the vagina at 35-37 weeks of gestation.
2. Escherichia coliis a gram-negativebacillusthat can cause neonatal meningitis and pneumonia.
3. Streptococcus pneumonia
4. Haemophilus influenza
5. Pneumonia in children [4 weeks-18 years]

In children ages 4 weeks to 18 years,common causes include viruses and bacteria such as a respiratory syncytial virus [RSV], mycoplasma, Chlamydia trachomatis [in infants], Chlamydia pneumonia [in young children and adolescents], and streptococcus pneumonia.

The respiratory syncytial virus can cause more severe infections in premature infants,which may present with high fever, and rapid breathing.Mycoplasma is a bacterium that causes atypical pneumonia also known as walking pneumonia. These bacteria commonly cause pneumonia in ages 4 weeks to 65 years.

Chlamydia pneumonia is a bacterium,spread through aerosols, causing atypical pneumonia, and presents with symptoms of short-lived fever,cough with little sputum production that may persist for several weeks.Chlamydiatrachomatis is a bacteriumthat can cause pneumonia in infants while passing through the birth canal with a characteristic of staccato cough.

Streptococcus pneumonia is a gram-positive bacterium that causes typical pneumonia and is a common cause of pneumonia in everyone > 4 weeks of age.

EPIDEMIOLOGY:

Pneumonia is the most common cause of serious illness and death in young children worldwide [11] Pneumonia is a widespread and common infectious lung disease that causes inflammation,which can lead to reduced oxygenation,shortness of breath, and death [12].Pneumonia is singly responsible for almost one-fifth of total mortality in vulnerable age groups. Therefore, the importance of pneumonia cannot be overemphasized.Consequently,global healthcare agencies such as the world health organization [WHO], the United Nations children's fund [UNICEF], national and state governments, as well as international and local agencies involved with aid, academics, and research have all focused on this area [13]. Community-acquired pneumonia [CAP] in children remains an important reason for hospital admission [14].Pneumonia accounts for 14% of all deaths of children under 5 years old, killing 740180 children in 2019[15].

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Pneumonia kills more children than any other infectious disease, claiming the lives of over 700,000 children under five every year, or around 2,000 every day. This includes over 200,000 newborns. Almost all of these deaths are preventable. Pneumonia affects more than 1,400 children worldwide every 100,000, or 1 child out of every 71, each year. The highest incidences are seen in South Asia (2,500 cases per 100,000 children) and West and Central Africa (1,620 cases per 100,000 children).

Progress in reducing deaths due to pneumonia in children under five has been significantly slower than for other infectious diseases. Since 2000, under-five deaths due to pneumonia have declined by 55 percent, while deaths due to diarrhea have decreased by 61 percent and are now almost half of the pneumonia deaths.[16].The World Health Organization [WHO] has developed standard case management guidelines to reduce the two million deaths, or 20 percent of all child deaths, caused by pneumonia through early diagnosis and treatment. A meta-analysis showed that these guidelines if effectively implemented, result in a significant reduction in mortality:24% [95% CI 14–33%] in total mortality and 36% [95% CI 20–48%] in pneumonia-related mortality in children aged 0 to 4 years in developing countries with infant mortality over 90 per 1,000 live births. Many countries have now adapted these guidelines as part of national acute respiratory infections control and Integrated Management of Childhood Illnesses [IMCI] programs.[17].

RISK FACTORS:

There is a wide variation in the risk factors for pneumonia,important risk factors associated with child pneumonia include a lack of exclusive breastfeeding, incomplete immunization, use of solid fuels in the household, overcrowding, low degree of maternal education,limited access to secondary care cigarette smoke and air pollution exposure,malnutrition and conditions of povertyand common comorbid conditions [18].Due to the linear relation of these risk factors, it is difficult to estimate their risk [19].

Some risk factors and clinical signs,including nutritional status,low birth weight, hypoxia,cyanosis, grunting, and radiological findings are the predictors of death in childhood pneumonia [20].Children with AIDS are at increased risk for community-acquired pneumonia, due in part to their defects in B-cell function [21].

CLINICAL PRESENTATION:

The clinical features vary by age of the patient and by the course of the illness. age influences the clinical presentation of pneumonia [22]. In all age groups, fever and cough are the hallmarks of pneumonia.The WHO successfully diagnoses pneumonia in children under the age of five using tachypnea and retractions, but as the child's age increases [in children >5 years], tachypnea becomes less sensitive and specific [23]. Neonatal pneumonia is suspected in any newborn infant with respiratory distress, the features of which include any of the following: rapid, noisy, or difficult breathing, respiratory rate >60 beats/min, chest retractions, cough, and/or grunting[24]Most of the clinical signs and symptoms have low sensitivity and specificity except for cough, crackles [rales], retractions, rhonchi, and nasal flaring [in young infants], which are highly specific but not sensitive, meaning that their absence might help rule out the disease[25].

TABLE 1. SIGNS AND SYMPTOMS

	NEONATES		INFANTS AND CHILDREN
1.	Fever	1.	Fever
2.	Irritability	2.	Cough
3.	Lethargy	3.	Abdominal pain
4.	Poor feeding	4.	Tachypnea
5.	Apnea	5.	Chest pain

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TABLE 2. TYPES OF SEVERITY:

CLINICAL FEATURES	SEVERITY
Altered sensorium, central cyanosis, convulsion, inability to feed, or severe respiratory distress	**Very severe pneumonia**
Lower Chest indrawing (LCI) and no signs of very severe pneumonia	**Severe pneumonia**
Fast breathing and no signs of severe /very severe pneumonia	**Non-severe pneumonia**
No signs of pneumonia or very severe pneumonia	**No pneumonia; cough or cold**

CRITERIAfor children with pneumonia who are experiencing respiratory distress:

Acute respiratory distress syndrome [ARDS] and pneumonia are closely correlated in critically ill patients. Whereas ARDS is often complicated by nosocomial pneumonia, pulmonary infection is also the most frequent single cause of ARDS [27].Several primary pulmonary and systemic disorders injure alveolar epithelium and increase the permeability of the alveolar-capillary barrier. Primary lung disorders that cause ARDS include pneumonia,aspiration, inhalation injuries, near-drowning, and contusions from trauma [28]. ARDS criteria in pneumonia include Tachypnea,Dyspnea,apnea,grunting,nasal flaring,altered mental status, pulse oximetry less than 90%, and retractions.

TABLE 3. DEPENDING ON AGE.

AGE	RESPIRATORY RATE [BEATS/MIN]
1. 0-2 months	**>60**
2. 2-12 months	**>50**
3. 1-5 years	**>40**
4. >5 years	**>20**

DIAGNOSIS:

Pneumonia is a clinical diagnosis based on history, and physical examination and can be confirmed by imaging studies.Consolidation and interstitial patterns, visualized using chest radiography or lung ultrasound, are characteristic features of pneumonia, although many guidelines only require imaging to diagnose pneumonia in ambiguous or hospitalized cases. For instance, the Pediatric Infectious Diseases Society does not recommend the use of chest radiography in community-acquired pneumonia unless the child is hypoxemic, in respiratory distress, has failed initial treatment, or is hospitalized [29].

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IMAGING STUDIES:

MRI with fast imaging sequences is comparable to chest radiographs for evaluating underlying pulmonary consolidation, bronchiectasis, necrosis/abscess, and pleural effusion often associated with pneumonia in children [30]., LUS may be considered the first imaging test in children with suspicion of CAP. In prospective research, a CAP diagnostic approach that incorporates LUS should be validated. Lung ultrasound can also be used for follow-up resolution of pneumonic lesions [31] Investigations often performed in children with pneumonia in industrialized countries include total white cell count and differential, procalcitonin, and inflammatory indicators such as erythrocyte sedimentation rate and C-reactive protein. Although a raised white cell count of over 15% 106/l with a predominance of band forms and an elevated C-reactive protein level may favor bacterial etiology, the sensitivity and specificity of these tests are highly variable. Some centers do not recommend routinely measuring them as they usually do not affect management. In conclusion, clinical suspicion is typically used to make the initial diagnosis of pneumonia, which may then be corroborated by specific radiological and potential laboratory findings.Not all features are present in any one child, and the emphasis on individual features may vary with age and likely etiology [32].

MANAGEMENT

Management of pneumonia starts with providing general supportive care including oxygen, fluid resuscitation, Incentive spirometry, and antipyretics.

Access the patient's need for hospital admission with the CURB-65 Score or the pneumonia severity index (PSI Score)

The PSI uses 20 clinical and investigational variables in its calculation to stratify patients into 5 severity classes with 30-d mortality ranging from <1% for classes I - III to 27% for class V. CURB-65 is an alternative severity scoring rule that assigns less importance to the impact of comorbidities and instead uses 5 variables (confusion, elevated blood urea, elevated respiratory rate, low systolic or diastolic blood pressure and age ≥65 y) to assign a 6-point score (05), where scores of 0-1, 2 and ≥3 correlate with low, intermediate and high short-term mortality, respectively.[33]

Startempiric antibiotics based on clinical presentation,severity, and risk factors of the patient, and then switch the therapy to a specific pathogen.[34]

TABLE 4. SITE OF CARE

SITE OF CARE	PRESUMED BACTERIAL PNEUMONIA	PRESUMED ATYPICAL PNEUMONIA	PRESUMED INFLUENZA PNEUMONIA
5 years old (preschool)	Amoxicillin, oral (90 mg/kg/day in 2 doses) Alternative: oral amoxicillin-clavulanate (amoxicillin component, 90 mg/kg/day in 2 doses)	Azithromycin oral (10 mg/kg on day 1, followed by 5mg/kg/day once daily on days 2–5).	Oseltamivir
5 years old	Oral amoxicillin (90 mg/kg/day in 2 doses to a maximum of 4 g/days); for children with presumed bacterial CAP who do not have a clinical, laboratory, orby 5 mg/kg/day once daily on days 2–5; Alternate medications include oral erythromycin (40 mg/kg/day in 4 doses) or clarithromycin (15 mg/kg/day in 2 doses for 7–14 days).	Oral azithromycin (10 mg/kg on day 1, followed by 5 mg/kg/day once daily on days 2–5 to a maximum of 500 mg on day 1, followed by 250 mg on days 2–5); alternatives: oral clarithromycin (15 mg/kg/day in 2 doses to a maximum of 1 g/day); erythromycin, doxycycline for children .7 years old	Oseltamivir or zanamivir (for children 7 years and older); alternatives: peramivir, oseltamivir, and zanamivirare under clinical investigation in children; intravenous zanamivir is available for compassionate use.

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Inpatient (all ages) Fully immunized with conjugate vaccines for Haemophilus influenzae type b and Streptococcus pneumoniae; local penicillin resistance in invasive strains of pneumococcus is minimal	Ampicillin or penicillin G; alternatives: ceftriaxone or cefotaxime; addition of vancomycin or clindamycin for suspected CA-MRSA	Azithromycin (in addition to b-lactam, if diagnosis of atypical pneumonia is in doubt); alternatives: clarithromycin or erythromycin; doxycycline for children .7 years old; levofloxacin for children who have reached growth maturity, or who cannot tolerate macrolides	Oseltamivir or zanamivir (for children $7 years old; alternatives: peramivir, oseltamivir, and zanamivir (all intravenous) are under clinical investigation in children; intravenous zanamivir available for compassionate use
Not fully immunized for H, influenza type b, and S. pneumoniae; local penicillin resistance in invasive strains of pneumococcus is significant	ceftriaxone or cefotaxime; addition of vancomycin or clindamycin for suspected CA-MRSA; alternative: levofloxacin; addition of vancomycin or clindamycin for suspected CA-MRSA	Azithromycin (in addition to b-lactam, if diagnosis in doubt); alternatives: erythromycin; doxycycline for children .7 years old; levofloxacin for children who have reached growth maturity or who cannot tolerate macrolides	Oseltamivir or zanamivir (for children 7 years old; alternatives: peramivir, oseltamivir, and zanamivir (all intravenous) are under clinical investigation in children; intravenous zanamivir available for compassionate use

OUTPATIENTS

Antimicrobial therapy is not routinely required for preschool-aged children with CAP, because viral pathogens are responsible for the great majority of clinical diseases. Amoxicillin should be used as first-line therapy for previously healthy, appropriately immunized infants and preschool children with mild to moderate CAP suspected to be of bacterial origin. Amoxicillin provides appropriate coverage for Streptococcus pneumoniae, the most prominent invasive bacterial pathogen. lists preferred agents and alternative agents for children allergic to amoxicillin should be used as first-line therapy for previously healthy appropriately immunized school-aged children and adolescents with mild to moderate CAP for S. pneumoniae, the most prominent invasive bacterial pathogen. Atypical bacterial pathogens (e.g., M. pneumonia), and less common lower respiratory tract bacterial pathogens, as discussed in the Evidence Summary, should also be considered in management decisions.

Children (mainly school-aged children and adolescents) examined in an outpatient environment with results consistent with CAP caused by atypical microorganisms should be treated with macrolide antibiotics. If M. pneumonia laboratory testing is available in a clinically appropriate time range, it should be done. lists recommended and suitable alternatives for treating unusual pathogens. Children with moderate to severe CAP consistent with influenza virus infection during widespread local influenza virus circulation should receive influenza antiviral therapy as soon as possible, especially if their condition is clinically worsening as seen by a visit to an outpatient facility.

Because early antiviral treatment has been shown to provide maximal benefit, treatment should not be delayed until confirmation of positive influenza test results. Negative results of influenza diagnostic tests, especially rapid antigen tests, do not conclusively exclude influenza disease. Treatment after 48 hours of symptomatic infection may still provide clinical benefit to those with more severe diseases.

INPATIENTS

When local epidemiology statistics show that there is not a significant high-level penicillin resistance for invasive, ampicillin or penicillin G should be given to the completely vaccinated infant or school-aged child admitted to a hospital ward with CAP. pneumoniae For hospitalized infants and kids who are not fully immunized, in areas where local epidemiology of invasive pneumococcal

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strains documents high-level penicillin resistance, or for infants and kids with a life-threatening infection, including those with empyema, empiric therapy with a third-generation parenteral cephalosporin (ceftriaxone or cefotaxime) should be prescribed.

For the level of resistance currently recognized in North America, non-lactam drugs like vancomycin are not any more successful at treating pneumococcal pneumonia than third-generation cephalosporins. Additionally, empiric combination therapy with a macrolide (parenteral or oral) When M. pneumoniae and C. pneumoniae are serious concerns for a hospitalized child, a b-lactam antibiotic should be provided; diagnostic testing, if accessible in a clinically appropriate time period, should be carried out. If clinical, laboratory or imaging features are consistent with an infection brought on by S. aureus, vancomycin or clindamycin should be administered in addition to b-lactam therapy.

II. CONCLUSION:

Pneumonia is a leading cause of morbidity and mortality in children younger than 5 years of age. Pneumonia has numerous potential etiologies, the most common of which is infectious, and effectively managed with the use of antibiotics. In the outpatient setting, antibiotic therapy for previously healthy without comorbidities or risk factors for resistant pathogens includes monotherapy with penicillin groups of antibiotics like amoxicillin or macrolides, combination therapy is suitable for patients with comorbidities or risk factors for resistant pathogens including anti-pneumococcal β-lactam antibiotic plus macrolide or doxycycline or monotherapy with respiratory fluoroquinolones. In the inpatient setting, for patients admitted in non-ICU, combination therapy includes anti-pneumococcal beta-lactam and macrolide or doxycycline monotherapy including respiratory fluoroquinolones. Combination therapy is suitable for patients with severe ICU admission including Anti-pneumococcal β-lactam plus macrolide or doxycycline or respiratory fluoroquinolones. For patients with penicillin allergy suitable drug of choice includes aztreonam plus respiratory fluoroquinolones.

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