

Review of Aetiology and Antibiotics Used in Community Acquired Pneumonia in Asia; A Preliminary Study for the Formulation of a Standard Treatment Guideline

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Abstract:-

Introduction: Pneumonia is a respiratory tract infection that makes breathing painful. It is one of the leading killers in the world, the largest victim being south asian countries. Pneumonia can be caused by a variety of pathogens and the detection of these pathogens takes a long time. The empirical therapy is given until the pathogen is detected but die to the absence of a standard guideline, the empirical therapy given in the treatment is not uniform and hence it is associated with high mortality. The purpose of the study is to review the aetiology of Pneumonia and the drugs effective in Pneumonia in Asian countries so as to facilitate the formulation of a local treatment guideline.

Result: The leading pathogens in the asian countries are found to be *S pneumoniae*, *S aureus*, *M pneumoniae* and *H influenzae*. *P aeruginosa* and *S aureus* were associated with higher mortality rates. The drugs used were mostly Beta lactams, Quinolones and Macrolides, either monotherapy or a combination therapy. Many cases of Macrolide resistance were seen.

Discussion and Conclusion: The use of macrolides were not associated to significant improvement in mortality rates, and since the macrolides were found to be highly resistant, they are not preferred for empirical therapy. Beta lactams particularly third generation cephalosporins are found to be highly used in the present context. Beta lactams or Quinolones monotherapy or a combination therapy can be effective for Community acquired Pneumonia.

Keywords:- Community Acquired Pneumonia, CAP, Empirical Therapy, Treatment Guidelines, *S Pneumoniae*, *S Aureus*.

I. INTRODUCTION

Pneumonia is an acute respiratory infection of lungs in which the alveolar sac is filled with pus and fluids which makes breathing painful and limits oxygen intake. (WHO) Most common pathogens causing pneumonia are *Streptococcus pneumoniae*, *Mycoplasma pneumoniae*, *Haemophilus influenzae*, *Pseudomonas aeruginosa*, *Staphylococcus aureus* and other respiratory viruses (1). However, different pathogens are found to be causing the disease with change in demography. Community acquired pneumonia (CAP) mostly common in children below 5 years of age. The prevalence of Pneumonia is 2500 cases per 100,000 among Asian population and accounts for 19% of all deaths of children under 5 years of age in South East Asia(2).

Combinations of β -lactam with macrolide or, monotherapy with fluoroquinolone are used as standard treatment for CAP (3). Empirical therapy is preferred by physician over target therapy for CAP as identification of causative organism takes time(4). Rationale prescription of antibiotics is needed as random use of antibiotics has led to increase in antimicrobial resistance.

Guidelines have been published by countries like the USA, UK, China, and India etc. for its treatment. Standard treatment guideline sets a protocol so that the use of drugs in the treatment of the disease is both ethical and effective and also reduces mortality and treatment failure. The four year study done in USA showed the reduction of mortality rate from 13.4 to 11% within the first month of the implementation of treatment guidelines(4).

Nepal also has Infectious disease control guidelines and National Antibiotics Treatment Guidelines but they don't provide sufficient idea on the standard approach to the Drug management of CAP. Thus, we need to form a local guideline that incorporates all the aspects of demography and

epidemiology along with locally resistant antibiotics and provides a clear approach to the management of Pneumonia.

II. METHODOLOGY

Preferred reporting items for systematic reviews and meta-analysis (PRISMA) (5) and protocol for reviews detailed in Cochranes handbook for systematic reviews of intervention (6) were followed for reporting the article.

Study identification

The systematic search was done on online data bases Pubmed, Clinical trials. org, EMBASE using the keywords “Pneumonia”, “antibiotics”, “Treatment guidelines”, “2015-2021”, “guideline” along with their name of all Asian countries connected with “OR” and “AND” boolean operator. References list of included trials and article were also searched to identify additional articles. The abstract was screened using Microsoft Excel 2013 (windows version) followed by full text screening. If there was only partial information available, concerned author were contacted via email.

Articles were included in the initial literature search if patient had pneumonia. The studies that recruited Asian population were only included in the study. Observational study and comparative study among multicenter were included in the review. The studies that were not available in English or the studies done on other animals were not included in this review. The studies which were carried out in a group of otherwise healthy patients, and analyzed the survival rate and

mortality within a time period were included in the study; the ones that only discussed the general prescription patterns were discarded. Similarly, randomized controlled trials were not included in the review. Case reports, review articles and other form of articles were excluded. Those studies which included western, African or European population were discarded for this review.

Data extraction

Two authors (SS and BSP) extracted the data from the included and studies and were recorded as follows:

- A. Author and year of study
- B. study period
- C. study methods
- D. study population
- E. age
- F. definition of pneumonia

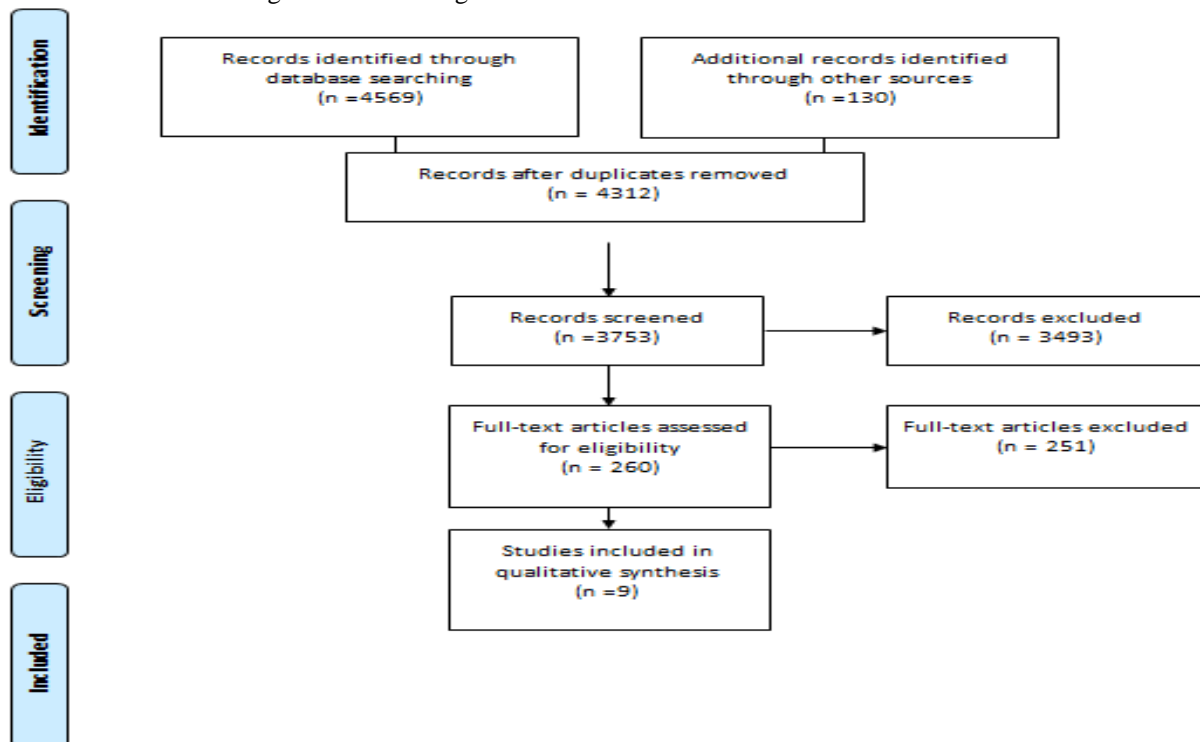
Extracted data was checked by another author (AG) and disagreement was resolved by discussion with other author (KKA). No any registered protocol was used for review.

III. RESULTS

Study selection

The literature search resulted in 4699 studies from PUBMED, EMBASE and clinical trials.org. After the complete screening process of titles, abstracts, and full texts, 4691 studies did not meet the eligibility criteria and nine articles with all different study design remained which was included in the review. A description of the flow of study selection is shown in the PRISMA flow diagram in figure 1.

Figure 1: PRISMA guidelines for article identification and selection



Of the included studies all the studies were retrospective, cross sectional and observational while study by Aykut ÇİLLİ et.al was prospective cohort. Studies sites of different Asian countries like Taiwan, Nepal, China, Japan, Korea, Vietnam and Turkey are included. Mean age group of patients, study duration of different studies are described in Table 1. Inclusion criteria of patient with pneumonia for the different studies are also described in Table 1. (7-15)

Author and year of study	Study period	Study methods	Study population	Age	Definition of pneumonia
Seok Gyun Haet. al, 2018	Jan 2015- Apr 2017	Retrospective	Korea; 190		1) signs and symptoms (fever, cough, dyspnea, productive sputum, chest pain, or abnormal breath sounds) of pneumonia; 2) abnormal chest X-ray findings compatible with pneumonia; and 3) identification of MP IgM antibody performed during the illness via enzyme-linked immunosorbent assay.
Bongyoung Kim et.al, 2020	2005-2010	Retrospective, Observational	Korea; 97,711	73 (46–83)	Adult (≥ 18 years) hospitalized patients with ICD-10 codes for all-cause pneumonia in the first or second priority discharge diagnosis
Chi-Chuan Wang et.al, 2016	2002-2011	Retrospective	Taiwan; 2622		Outpatient visit with a primary diagnosis of pneumonia (The International Classification of Diseases, Ninth Revision, Clinical Modification) and a confirmatory diagnostic procedure, such as chest X-ray, sputum culture, or blood culture
Jun Suzuki et.al, 2019	2010-2015	Retrospective	Japan; 1999		Pneumonia was identified by ICD-10 codes J13eJ18 as the primary diagnosis Severe pneumonia was defined as patients diagnosed with pneumonia who required vasopressors and/or mechanical ventilation within 2 days after admission, according to the Infectious Diseases Society of America/American Thoracic Society Consensus guideline
Hieu T. Trinh et.al, 2014	2010	Retrospective	Vietnam; 649	68 (51–79)	Adults aged 16 years and older, admitted for at least 24 h with a primary diagnosis of bacterial pneumonia acquired in the community
Masato Tashiro et.al, 2017	2010-2013	Retrospective, cross sectional	Japan; 1605	Macrolide (49.7 \pm 22.4), quinolone (50.5 \pm 20.7), tetracycline (50.6 \pm 24.0)	We included patients who were aged ≥ 18 years and who had undergone diagnostic testing (paired antibody titers, polymerase chain reaction, and antigen detection) to confirm <i>M. pneumoniae</i> infection. Single measurements of antibody titer and cold agglutinin tests were not included as diagnostic tests in this study because those are not specific tests for <i>M. pneumoniae</i> infection.
Aykut ÇİLLİ et.al, 2018	2009-2013	Prospective cohort study	Turkey; 621	64.3 \pm 16.9	Adults (age > 18 years) patients with symptoms and signs of lower respiratory tract infection with a new pulmonary infiltrate on the admission chest radiograph, and whose discharge diagnosis was CAP, were included

Ali Khawaja et al, 2013	2002-2008	Retrospective Cross sectionsl study	Pakistan; 189	60 ± 18.0	A retrospective cross-sectional study was conducted from March 2002 till December 2008 on patients of 16 years and above who were admitted with the diagnosis of SCAP in accordance to the criteria of American Thoracic Society Guidelines
Bhishma Pokhrel et. Al.	2017-2019	Cross sectional study	Nepal; 659		For this study, we defined CAP as "an acute infection of the pulmonary parenchyma that is associated with some symptoms of acute infection, accompanied by the presence of an acute infiltrate on a chest radiograph or auscultatory findings consistent with pneumonia in a patient not hospitalized or residing in a long-term care facility for more than 14 days before the onset of symptoms" as per IDSA guideline

Table 1- Selected studies

The predominantly found pathogens in the area are *S. pneumoniae*, *S. aureus*, *M. pneumoniae*, *K. pneumoniae*, *H. influenzae*, *P. aeruginosa*. The detailed description of the pathogens along with their associated mortality is given in Table 2.

Aetiology	Number of studies	Range %	Highest mortality %
<i>S pneumoniae</i>	4	7-32%	29%
<i>H influenzae</i>	2	12- 20%	-
<i>M pneumoniae</i>	2	10-30%	12%
<i>S aureus</i>	3	12- 34%	53%
<i>P aeruginosa</i>	3	7-11%	89%
<i>K pneumoniae</i>	1	<5%	50%

Table 2 - Result: Aetiology of Community Acquired Pneumonia

The literature from different studies across South Asia showed that the mostly used antibiotics are Beta lactams and quinolones/ fluoroquinolones in CAP. Macrolides are also used in considerable cases. Likewise, tetracyclines and aminoglycosides combined with Cephalosporins are also among the widely used drugs. In case of macrolide resistance, quinolones and tetracyclines have been used. The list of antibiotics used in the selected studies is given in Table 3.

Anyibiotics	Number of studies
Macrolides Mono Therapy	2
Quinolones Mono Therapy	4
Beta lactams Mono Therapy	3
Beta lactams + Macrolides	3
Beta lactams + Quinolones	2
Tetracyclines	2
Carbapenems	1

Table 3- Result : Use of different antibiotics in the study

The comparative study done by Chi- Chuan Wang showed that fluoroquinolones were better than penicillin antibiotics regarding treatment failures. Jon Suzuki did a study of two groups of antibiotics and concluded that there were no significant difference in treatment failures and mortality when treated with Azithromycin in combination with Beta Lactams or Levofloxacin in combination with Beta lactams. A comparison among Beta lactams mono therapy, Beta lactams combination with macrolides and fluoroquinolones was done by Aykut et al in which there was no significant changes in mortality and treatment failures. However, a study of quinolones combined with tetracyclines in macrolide resistant *Mycoplasma pneumoniae* patients by Masato Tashiro. et al showed no significant difference in LOS and mortality when treated with either antibiotics.

The Study done by Seok Gyun et. al. and Bhishma Pokhrel et. al. was on children. In Seok Gyuns study, 16% of the total patients with CAP were resistant to Macrolides altogether. The study done in Nepal by Bhishma Pokhrel and group concluded that the patients treated by ampicillin were likely to be switched to secondary therapy compared to those treated with Ceftriaxones. The conclusions and outcomes of the selected studies is given in Table 4.

Author	Drugs used	Conclusion
Bongyoung Kim et.al, 2020	Macrolides Fluoroquinolones Carbapenems Cephalosporins	Increase in use of 4 th generation Cephalosporin and Carbapenems in recent years
Chi-Chuan Wang et.al, 2016	Penicillins Fluoroquinolones	Fluoroquinolones were better in terms of treatment failure, compared to penicillin therapy
Jun Suzuki et.al, 2019	Azithromycin+ Beta lactam Levofloxacin + Beta Lactam	No significant difference in mortality and treatment failures
Hieu T. Trinh et.al, 2014	Aminoglycosides + C3G Macrolides +C3G Quinolones+ C3G	Increased nationwide use of 3 rd Generation Cephalosporins monotherapy or combination therapy
Aykut ÇİLLİ et.al, 2018	Beta lactam monotherapy Beta lactam + macrolides Fluoroquinolones	No significant difference in treatment or survival rates in any of the three therapies.
Seok Gyun Ha et.al, 2018	Doxycycline Levofloxacin	16% patients were unresponsive to macrolides and were switched to other drugs, all of which could not show significant improvement
Bhishma Pokhrel et al.	Ampicillin monotherapy Ceftriaxone monotherapy	Patients treated with ampicillin were more likely to be switched to secondary therapy compared to those treated with ceftriaxone.
Masato Tashiro et.al, 2017	Quinolones Tetracyclines	No significant difference in LOS and mortality in both Quinolone and Tetracycline therapies

Table 4- Result: Outcomes in included studies

IV. DISCUSSION

CAP is one of the leading killers of childhood deaths worldwide. An estimated 2 million deaths occur yearly due to community-acquired pneumonia (CAP) in children < 5 (16). Every year, approximately 43 million new cases of pediatric pneumonia are reported in India. Poor and delayed care-seeking has been implicated in 6–70% of child deaths in developing countries, including those from pneumonia(17,18).

The type of antibiotics used to treat CAP mostly depends on empirical therapies due to difficulties in isolating the causative pathogens. Accordingly, guidelines for empirical therapies influence the selection of antibiotics for CAP. Fluoroquinolone alone or beta-lactam combined with macrolide is preferred 1st line therapy against CAP. These regimens were effective for *Streptococcus pneumoniae* and *Mycoplasma pneumoniae* which were the most common causative agents of CAP. However, macrolide is not preferred; because no significant difference was seen in the treatment outcomes between beta-lactam alone and beta-lactam combined with macrolide. The most commonly prescribed antibiotic classes are 3rd generation cephalosporins, macrolide, and Beta lactams. The increasing number of *S aureus* is a surprise as compared to the data from Western Countries and demands for the change in empirical therapy. A suitable broad spectrum antibiotic for *S aureus* as a part of the treatment regimen is a necessity.

The use of beta-lactam and macrolide is preferred to fluoroquinolone as fluoroquinolone for patients with CAP might delay the diagnosis of tuberculosis and increase the risk of antibiotic resistance.(19) The US Food and Drug Administration has been warning about fluoroquinolone usage since 2008 due to the risk of tendinitis, aortic rupture, QT prolongation, etc. The causative organisms of CAP in older patients tend to be polymicrobial with gram-negative bacteria, particularly in those who have a chronic pulmonary disease and also aspiration is an important mechanism of CAP in older adults, especially in those with cognitive or functional impairment. Hence, higher amount of broad-spectrum antibiotics for older patients is prescribed.

V. CONCLUSION

Community acquired pneumonia is a life threatening infection and demands proper use of antibiotics for its cure. The empirical therapy for this infection should be chosen so that it covers all the possible pathogens and also has a better survival ratio than other of its type. A committee should be formed including the experts in the matters and a Treatment Guideline should be formulated that puts and end to haphazard use of antibiotics in CAP and also decreases the mortality rate. The national data on antimicrobial resistance and isolated pathogens should be compared to form the guideline at the earliest.

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