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Review Article

Systematic review on prescribing trends of antibiotics in community acquired pneumonia

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ABSTRACT

Community acquired pneumonia is one of the leading cause for death in the world. The study evaluates the prescribing trends of antibiotics in the management of community acquired pneumonia (CAP) and in assessing the antibiotic culture sensitivity pattern. The study highlights the usage of antibiotics rationally to prevent antibiotic resistance so that the antibiotic agents are preserved for future patients. A systematic review was conducted according to the Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA). The investigators independently performed the literature review and screened the articles for relevance and eligibility. The most common gram positive microorganism was *Streptococcus pneumoniae* and the common gram negative microorganism was *Klebsiella pneumoniae. Streptococcus pneumoniae* is almost resistant to macrolides. The most common dual therapy prescribed to the study patients were beta-lactam combined with macrolides. The study emphasizes the importance of proper selection of antibiotics to prevent the increased incidence of antibiotic resistance.

Key words: Prescribing pattern, Resistance pattern, Antibiotics, Gram positive bacteria, Gram negative bacteria.

INTRODUCTION

Pneumonia is defined as the inflammation of the lung parenchyma of the alveoli rather than the bronchi or bronchioles, of infective origin and characterized by consolidation [1]. Community acquired pneumonia (CAP) is one of the most common causes of morbidity and mortality in both adults and children [2].

Antibiotics have saved millions of lives across the globe from the time of their invention. Today, we cannot imagine a day without antibiotics. Unfortunately, today due to the overuse, abuse and misuse of antibiotics, resistant bacteria have surfaced to cause increased mortality and morbidity. In the battle between microbes and antibiotics, the microbes have often won many battles as the resistance pattern has travelled from

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simple drug resistance to Multidrug Resistance (MDR) to Total Drug Resistance (TDR) [3]. As the microorganism become resistant to first-line antimicrobials, the high cost of the second-line drugs may result in failure to treat these diseases. Most alarming of all is the diseases caused by multidrug-resistant microbes, which are virtually non-treatable and thereby contributes to a "post-antibiotic era". Inappropriate antimicrobial use is associated with the emergence of resistance. In addition, the misuse of antibiotics contributes to the growing problem of antimicrobial resistance and is considered as a most serious threat to public health. An effective antimicrobial stewardship program with appropriate, drug selection, dosing, route of administration and duration of antimicrobial therapy coupled with comprehensive infection control program has shown to limit the emergence and transmission of antimicrobial resistant pathogens [4]. Implementing the standard treatment guidelines (STGs) is one of the important tools to promote rational use of antibiotics [5]. Given the emergence of antibiotic resistance and the potential hazards of antibiotic treatment failures, a definitive microbiological diagnosis is desirable [6]. Rational drug use take place when the drug prescribed is appropriate, affordable, available, dispensed correctly and correct doses at adequate time intervals [7]. The study aims in reviewing the antibiotics prescribed in the management of community acquired pneumonia (CAP).

METHODOLOGY

Study design: A systematic review was conducted according to the Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA). Investigators independently performed the literature review and screened the articles for relevance and eligibility.

Search strategy: Pubmed and Google scholar from December 1998 until October 2017 were queried to identify studies that reported the prescribing pattern of CAP using a combination of <pneumonia>, <CAP> OR <community acquired pneumonia>, <prescribing pattern> OR <prescribing trends>, <bacteriology>, <antibiotic resistance>, <causative agent> OR <pathogen>, <antibiotic therapy>, <antibiogram> OR <antibiotic susceptibility>, <Prescribing pattern> AND <Resistance pattern> as search terms. 'related articles' as well as articles referenced by those that came up in the search were reviewed.

The titles and abstract of articles were scrutinized for relevance and accessed the full-text of relevant articles which were screened for eligibility. The bibliographies of eligible articles were further examined for potentially relevant studies.

Study selection: This systematic review was confined to original articles in the English language on confirmed cases of CAP. The articles that provided sufficient information to determine the prescribing pattern of antibiotics, finding the causative agent, either by blood/sputum culture and antibiogram that were available at the time of the study. The studies of elderly subject were included because majority of patients who develop CAP are older adults. The following studies were excluded which focused on a single pathogen, paediatric population, studies that were performed during a specific outbreak such as the recent COVID-19 pandemic, or those that focused on a specific population. Case reports, commentaries were also excluded.

Data abstraction: Data was extracted from each article and the extracted data was included in individually designed tabular columns as place of study, study population, study design, sample size, number of blood/sputum culture done, number of patients with an identified microbiologic etiology, the antibiotic culture sensitivity pattern, whether the antibiotic is sensitive/ resistant, the prescribing pattern of antibiotics, as mono, dual or triple antibiotic therapy.

Outcome measures: The primary endpoint of this systematic review was whether the culture of blood/sputum was done or not, the data regarding culture sensitivity pattern of antibiotics was assessed and the most common micro-organism and the most sensitive/resistant antibiotic were extracted. The type of therapy given to the patients was assessed and the data is compiled.

RESULTS AND DISCUSSION

The data illustrated in Table 1 is that in about five studies all the patients have undergone sputum/blood culture test. But the remaining studies that did not undergo culture test, treatment was initiated based on radiological investigation such as X-ray, CT scan and clinical presentation. Culture test was not carried out in few patients as they have consumed antibiotic prior to admission. A large percentage of patients with pneumonia, sputum culture was negative. The reasons for this were, sick patients with altered sensorium unable to expectorate and non-productive cough and thus unable to expectorate a satisfactory sputum sample [13]. It is essential for patients who are diagnosed with community acquired pneumonia to undergo culture test to find out the microorganism and then to de-escalate the empirical antibiotic therapy to definitive therapy.

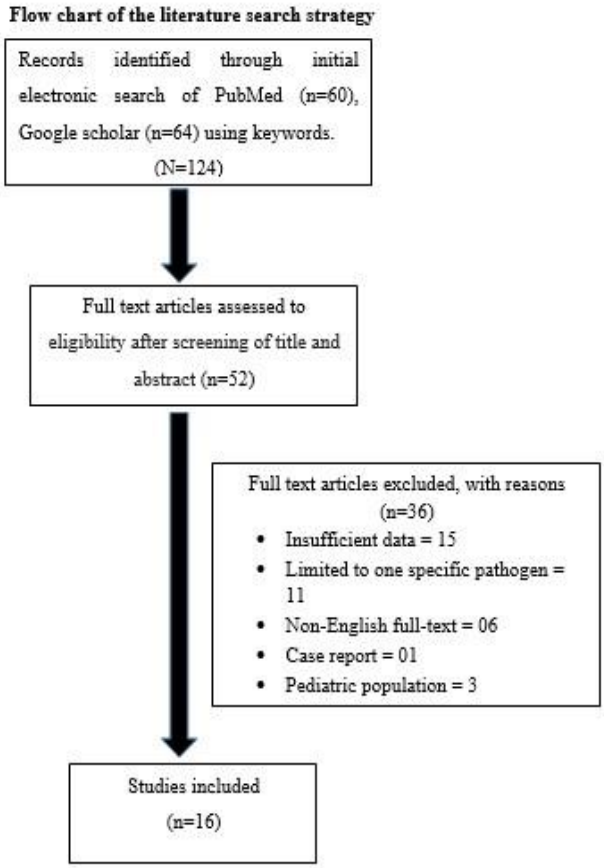

TABLE 1: SUMMARY OF CULTURE TEST

Author and year	Place of study	Study design/ Sample size	Culture		
			Yes	No	Biological sample
Leela Prasad Babu K et al, 2019 [8]	Andra pradesh, India	Prospective Observational/ 120 patients	n=65 (54.17%)	n=55 (45.83%)	Sputum
Reyaz. A Para et al, 2018 [9]	Srinagar, India	Prospective/ 225 patients	n=162 (72%)	n=63 (28%)	Sputum
Saeed et al, 2017 [10]	Kingdom of Saudi Arabia	Cross-sectional retrospective/ 117 patients	n=50 (42.73%)	n=67 (57.26%)	Sputum
Kodur Ramamurthy et al, 2016 [3]	Bangalore, India	Cross sectional/ 268 Patients	n=188 (70.14%)	n=80 (29.85%)	Sputum
Kotwani, 2015 [11]	New Delhi, India	Cross-sectional retrospective/ 261 patients	n=97 (37.16%)	n=164 (62.83%)	Sputum
Sonia Akter, 2014 [12]	Mangalore, India	Cross sectional/ 105 Patients	n=105 (100%)	-	Blood/Sputum
Vishak K Acharya, 2014 [13]	Dhaka, Bangladesh	Cross sectional/ 100 Patients	n=100 (100%)	-	Sputum

Harish Govind Naik et al, 2013 [14]	Maharashtra, India	Non-Interventional retrospective observational/ 51 patients	n=23 (45.09%)	n=28 (54.90%)	Sputum
Regasa et al, 2012 [15]	Ethiopia	Cross sectional/ 133 patients	n=133 (100%)	-	Sputum
Bashir Ahmed Shah et al, 2010 [16]	Srinagar, India	Prospective/100 patients	n = 29 (29%)	n = 71 (71%)	Blood/Sputum
Menon et al, 2009 [6]	Kerala, India	Prospective/ 145 patients	n=145 (100%)	-	Sputum
Afia Zafar et al, 2008 [17]	Karachi, Pakistan	Prospective/ 200 patients	n=153 (76.5%)	n= 47 (23.5%)	Blood/Sputum
Aroma Oberoi et al, 2006 [18]	Ludhiana, Punjab, India	Prospective/ 233 patients	n=233 (100%)	-	Blood/Sputum

In the table 2 we can observe that the most prevalent micro-organism in community acquired pneumonia was *Streptococcus pneumoniae* followed by *Klebsiella pneumoniae* and *Pseudomonas aeruginosa*. Among the 10 studies, 9 studies reported that *Streptococcus pneumoniae* as the most prevalent gram positive micro-organism, only one study reported *Staphylococcous aureus*. And regarding the gram negative micro-organism, *Klebsiella pneumoniae* and *Pseudomonas aeruginosa* were equally prevalent among the studies. *Streptococcus pneumoniae* has been identified as the commonest organism causing community acquired pneumonia (CAP) all over the world [16]. Whereas, in Indian studies over the last three decades have reported higher incidence of gram negative organism among culture positive pneumonia [18]. In Literature review of Indian studies, gram negative organism *Pseudomonas aeruginosa* was prevalently found in the northern states population and gram negative *Klebsiella pneumoniae* was more prevalent in southern Indian population. It was noted that the reporting of the causative micro-organism is limited due to prior use of antibiotics and decreased sputum production.

TABLE 2: MOST PREVALENT GRAM POSITIVE AND GRAM NEGATIVE MICRO-ORGANISM

Author and year	**Place of study**	**Study design and Sample size**	**Micro Organism**		**Others**
			Gram +ve	**Gram -ve**	
Reyaz. A Para et al, 2018 [9]	Srinagar, India	Prospective/ 225 patients	*Streptococcus pneumoniae* n=61 (30.5%)	*Legionella Pneumophilia* n=33 (17.5%)	*Mycoplasma* n=13 (7.2%) *Influenza virus* n=13 (15.4%) *Chlamydi*a n=10 (5.5%) *Klebsiella pneumoniae* n=11(4.8%)
Prasad P et al, 2017 [19]	Karnataka, India	Cross sectional/ 165 patients	*Streptococcus pneumoniae* 13.33%	*Klebsiella pneumoniae* 29.09%	*Pseudomonas species* 18.18% *Haemophilus influenzae* 4.8%
Kodur Ramamurthy et al, 2016 [3]	Bangalore, India	Cross sectional/ 268 Patients	*Streptococcus pneumoniae* n =44 (42.30%)	*Klebsiella Pneumoniae* n =10 (9.61%)	Other *streptococcus species* n=16(15.38%) *Stephylococus aureus* n=12 (11.53%) *Pseudomonas species* n=8 (7.69%)

Vishak K Acharya et al, 2014 [13]	Dhaka, Bangladesh	Cross sectional/ 100 Patients	*Streptococcus pneumoniae* n =12 (31%)	*Pseudomonas aeruginosa* n =6 (15%)	*Klebsiella pneumoniae* n=5 (13%) *Staphylococcus aureus* n=3 (8%)
Sonia Akter et al, 2014 [12]	Mangalore, India	Cross sectional/ 105 Patients	*Streptococcus pneumoniae* n=20 (19.05%)	*Klebsiella pneumoniae* n=14 (13.33%)	*Haemophilus influenzae* n=9(8.57%) *Pseudomonas aeruginosa* n=6(5.71%) *Escherichia coli* n=3 (1.09%)
Regasa et al, 2012 [15]	Ethiopia	Cross sectional/ 133 patients	*Streptococcus pneumoniae* n =17 (12.8%)	*Pseudomonas aeruginosa* n =9 (6.8%)	*Staphylococcus aureus* n=14 (10.5%) *Klebsiella pneumoniae* n=7 (13.33%)
Bashir Ahmed shah et al, 2010 [16]	Srinagar, India	Prospective/ 100 patients	*Staphylococcus aureus* n=7 (24.1%)	*Pseudomonas aeruginosa* n= 10 (34.4%)	*Escherichia coli* n=6 (20.6%) *Klebsiella pneumoniae* n=3 (10.3%)
Menon et al, 2009 [6]	Kerala, India	Prospective/ 145 patients	*Streptococcus pneumoniae* n =36 (32.41%)	*Klebsiella pneumoniae* n =22 (20%)	*Pseudomonas aeruginosa* n= 9(8.97%) E.coli n=7 (6.21%)
Afia Zafar et al, 2008 [17]	Karachi, Pakistan.	Prospective/ 200 patients.	*Streptococcus pneumoniae* n=100(50%)	*Haemophilus influenzae* n=100 (50%)	-
Aroma Oberoi et al, 2006 [18]	Ludhiana , Punjab, India	Prospective/ 233 patients	*Streptococcus pneumoniae* n=22(32.8%)	*Pseudomonas aeruginosa* n=10 (24.3%)	*Staphylococcus aureus* n=8(19.5%) *Klebsiella pneumoniae* n=4(9.7%)

In table 3, we can observe that the *Streptococcus pneumoniae* was more sensitive to amoxyclav, levofloxacin and it is resistant to oxacillin, azithromycin, clarithromycin and erythromycin (macrolides). This shows that *Streptococcus pneumoniae* is almost resistant to macrolides. In an another study fluoroquinolones were found to be resistant hence high end antibiotics such as linezolid was given and it was found to be sensitive. In one study population, as *Staphylococcus aureus* was resistant to amoxicillin hence cephalosporins was prescribed and it was found to be sensitive.

TABLE 3: ANTIBIOTIC CULTURE SENSITIVITY PATTERN OF GRAM POSITIVE MICROORGANISM

Author and year	**Place of study**	**Study design/ Sample size / Site of treatment**	**Antibiotic culture sensitivity**		
			Gram + ve		
			Organism	**Sensitive**	**Resistance**
Prasad P et al, 2017 [19]	Karnataka, India	Cross sectional/ 165 patients / Inpatients	*Streptococcous pneumoniae*	Amoxiclav (80%), Levofloxacin (80%)	-
Kodur Ramamurthy et al, 2016 [3]	Bangalore, India	Cross sectional/ 268 Patients / Inpatients	*Staphylococcus aureus*	Ciprofloxacin (50%), Ofloxacin (50%)	Amoxicillin (88.33%), Azithromycin (88.33%)

Sonia Akter et al, 2014 [12]	Mangalore, India	Cross sectional/ 105 Patients / Inpatients	*Streptococcous pneumoniae*	Amoxyclav (95%), ampicillin (85%), levofloxacin (70%)	Azithromycin (65%), Cefixime (50%)
Regasa et al, 2012 [15]	Ethiopia	Cross sectional/ 133 patients / Inpatients	*Streptococcous pneumoniae*	Tetracycline (35%)	Oxacillin (55%)
Menon et al, 2009 [6]	Kerala, India	Prospective/ 145 patients / Inpatients	*Streptococcous pneumoniae*	Linezolid (82.5%),	Levofloxacin (0.69%)
Afia Zafar et al 2008 [17]	Karachi, Pakistan.	Prospective/ 200 patients / Inpatients	*Streptococcous pneumoniae*	Amoxicillin (100%) Levofloxacin (97%)	Erythromycin and clarithromycin (28%)

In the table 4, we can notice that *Haemophilus influenzae* was sensitive to cephalosporins, macrolide and meropenem. *Klebsiella pneumoniae* was sensitive to amikacin and meropenem. *Pseudomonas aeruginosa* was sensitive to ceftriaxone, ciprofloxacin. Cephalosporins were more sensitive with gram negative micro-organism.

TABLE 4: ANTIBIOTIC CULTURE SENSITIVITY PATTERN OF GRAM NEGATIVE MICROORGANISM

Author and year	**Place of study**	**Study design/ Sample size/ Site of treatment**	**Antibiotic culture sensitivity**		
			Gram - ve		
			Organism	**Sensitive**	**Resistance**
Prasad P et al, 2017 [19]	Karnataka, India	Cross sectional 165 patients / Inpatients	*Haemophilus Influenzae*	Amoxiclave (77%), Azithromycin (87%) Cefuroxime (94%)	-
Kodur Ramamurthy et al, 2016 [3]	Bangalore, India	Cross sectional/ 268 Patients / Inpatients	*Pseudomonas aeruginosa*	Gentamycin (25%)	Cefixime (81.2%)
Sonia Akter et al, 2014 [12]	Mangalore, India	Cross sectional/ 105 Patients / Inpatients	*Klebsiella pneumonia Haemophilus Influenzae*	Meropenam (100%) Meropenam (100%)	Clarithromycin (57.14%) Ciprofloxacin (88.8%)
Regasa et al, 2012 [15]	Ethiopia	Cross sectional/ 133 patients / Inpatients	*Pseudomonas aeruginosa*	Ceftriaxone 2 (20%) and Ciprofloxacin 2 (20%).	Gentamycin 5 (50%).
Menon et al, 2009 [6]	Kerala, India	Prospective/ 145 patients / Inpatients	*Klebsiella pneumoniae*	Amikacin	-
Afia Zafar et al 2008 [17]	Karachi, Pakistan.	Prospective/ 200 patients / Inpatients	*Haemophilus Influenzae*	Cefixime (100%) Clarithromycin (98%)	-

The data illustrated in Table 5 indicates that highest number of patients received dual therapy followed by mono therapy and then triple therapy. The most common dual therapy prescribed to the above study patients were beta-lactam combined with macrolides. Patients with co-morbidities such as other respiratory disease, diabetes mellitus, cardiovascular disease are treated with dual and triple therapy rather than monotherapy [10]. The prescribing pattern of antibiotics in patients is altered due to presence of some co-morbid conditions. It is observed that the most common co-morbid condition was chronic obstructive pulmonary disease (COPD) and according to Indian guidelines for CAP treatment, the most preferred choice of antibiotic combination drug is piperacillin + tazobactum and macrolide/doxycycline. Hence the dual antibiotic treatment given to community acquired pneumonia patient in the studies selected was in correlation with the Indian treatment guidelines.

TABLE 5: ANTIMICROBIAL MANAGEMENT IN COMMUNITY ACQUIRED PNEUMONIA

Author and year	Place of study	Study design/ Sample size	Therapy		
			Mono	Dual	Triple
Leela Prasad Babu K et al, 2019 [8]	Andra pradesh, India	Prospective Observational/ 120 patients	n =7 (5.83%)	n =97 (80.83%)	n =16 (13.33%)
Saeed et al, 2017 [10]	Kingdom of Saudi Arabia	Cross-sectional retrospective 117 patients	n =51 (43.58%)	n =57 (48.71%)	n =9 (7.69%)
Chandra Narayan Gupta et al, 2017 [20]	Haldia, West Bengal, India	Retrospective observational/ 200 patients	n = 15 (75%)	n = 5 (25%)	-
Kotwani et al, 2015 [11]	New Delhi, India	Cross-sectional retrospective 261 patients	n =33 (12.64%)	n =183 (70.11%)	n =45 (17.4%)
Kumar et al, 2015 [21]	Bhubaneswar, India	Prospective observational/ 117 patients	n =59 (55.55%)	n =52 (44.4%)	-
Harish Govind Naik et al, 2013 [14]	Maharashtra, India	Non - Interventional retrospective observational/ 51 patients	n =13 (25.49%)	n=38 74.51% (Poly antibiotic therapy)	

CONCLUSION

This systematic review of literatures on patients clearly highlights the culture sensitivity and the prescribing pattern of antibiotics in the management of community acquired pneumonia. In all the studies treatment was based on culture test except in few patient's treatment was based on radiological examinations such as X ray, CT scan, serological test and clinical presentation. Among the 10 included studies in management of CAP, 9 studies reported that *Streptococcus pneumoniae* was the most common causative micro-organism for CAP followed by *Klebsiella pneumoniae*. The *Streptococcus pneumoniae* is more sensitive to Beta-lactams, whereas it is almost resistant to macrolides and oxacillin. In case of gram negative bacteria, *Haemophilus influenzae* was sensitive to cephalosporins and macrolides and resistant to fluoroquinolones. *Klebsiella pneumoniae* was sensitive to amikacin and meropenem. The most common therapy prescribed to the above study patients were beta-lactam combined with macrolides. The outcomes of this study helps us to start empiric antibiotic treatment upon patient admission in hospital based on the prevalence of micro-organism since culture results take some time to be reported. This helps in reducing the morbidity and mortality to a certain extent in CAP patients.

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