

Community acquired pneumonia in Pakistan: An analysis on the literature published between 2003 and 2013

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Abstract

This article reviews literature pertaining to community acquired pneumonia (CAP) in adults published over the last decade (2003-2013) and includes ten studies and one guideline document. The review was done to identify the trend in etiologies and antimicrobial susceptibilities in order to recognize the need to update treatment guidelines for CAP in adults.

Except for one laboratory based study, no articles were published between 2003 and 2008. Thereafter, most of the studies are retrospective in nature and published with a time lag hence reducing the relevance of the data. Out of the ten studies, two were purely clinical and among those that presented microbiological data, sensitivities to antibiotics were demonstrated in five studies which too were mainly organism specific. *Streptococcus pneumoniae* remains the most common etiology of CAP in adults. There is increased isolation of atypical organisms in mild to moderate CAP, possibly due to better detection techniques. Mortality related to CAP is on the rise and noted up to 51% in patients with severe disease.

There is limited evidence to support increasing resistances of pathogens to antibiotics. Lack of updated data leaves Pakistan Chest Society guidelines 2010 for treatment of CAP applicable to date in its original form. However there is a need to conduct more comprehensive studies on CAP to help reduce morbidity and mortality associated with the disease.

Keywords: Bacterial Pneumonia, Community Acquired Infections.

Introduction

There is a general impression that there is great paucity of data on community acquired pneumonia (CAP) in Pakistan. To determine the factual status, we decided to look into the evidence regarding this issue with the following objectives:

- ◆ to identify the trend of CAP, its etiology and sensitivities

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- ◆ to determine whether the available data is adequate to derive conclusions and modify current guidelines

- ◆ to identify the limitations and inconsistencies in the available literature in this regard

- ◆ to help understand what is required of us to reach ideal standards in this type of reporting pertaining to CAP and to create interest in young researchers to explore this aspect of pulmonary medicine

With this in mind, all relevant articles were identified via PubMed/Medline using the keywords "Community Acquired Pneumonia", "Antimicrobial Resistance", and "Antibiotic susceptibility". Articles that were published in print and online, during the last decade 2003-2013 in Pakistan were included. Although special attention was given to the selection of articles, such a review cannot be exhaustive. We were able to identify and review eleven published articles including one published guideline. All the studies were closely analyzed with regard to their positive aspects and limitations. The results are summarized individually as well as in totality to give the reader an overview of the status of published literature on CAP in Pakistan over the last decade.

Review

The first laboratory based observational study was conducted in Rawalpindi between 2002 and 2003.¹ The study demonstrates a low diagnostic yield for isolated pathogens 88 out of 510 specimens (17.25%). Most commonly identified pathogen was *Haemophilus influenzae* (HI) with a strikingly high relative frequency (64 out of 88) among isolates. However, this yield is reported in a majority of paediatric population (41 out of 64) with 33 being less than five years of age. These figures therefore will not be in any way reflective of adult CAP status.

The most comprehensive study was The Active Study.² This study was conducted as a part of an international survey that included nine countries from all over the world. This contribution from Pakistan comprised of 200 samples. SP and HI were almost equally identified in CAP cases (90 and 87 respectively). Macrolide showed poor sensitivity against SP with 28% being resistant to

erythromycin and clarithromycin. Resistance to levofloxacin was detected in 3% of SP tested in this study. All were sensitive to beta lactams. Fluoroquinolones and cephalosporins were found to be consistently active against HI tested in this study. Although beta lactamase producing HI is an emerging problem all over the world the results of this study suggest that beta lactamase producing strains of HI are less prevalent in Pakistan as all the isolates were sensitive to beta lactams, macrolides and cephalosporins with a very low level resistance to ampicillin (3%).²

An observational retrospective study was conducted at a tertiary care hospital, where clinical and radiological presentations and laboratory investigations were part of inclusion criteria in an attempt to predict mortality in patients hospitalized with CAP.³ In addition to the risk factors stated in CURB-65 score recommended by the British Thoracic Society, increased mortality was found in patients having abnormal liver function tests, low serum albumin and presence of cardiomegaly at the time of admission. Out of 329 cases, overall mortality was 36 (11%). Nevertheless, failure to respond to treatment, development of complications such as multi organ failure, septic shock, ARDS, and need of ventilatory support, were strongly associated with increased mortality. There was a low yield in microbiological specimens with no pathogen identified in two-thirds of the patients which could be attributed to the non-availability of serological tests for atypical pathogens such as *Mycoplasma* and *Chlamydia pneumoniae*. Among the organisms identified in respiratory specimens, SP was the single most commonly found (8.3%), followed by gram negative organisms such as *Pseudomonas aeruginosa*, *Acinetobacter*, *Escherichia coli* (*E.coli*) and *Klebsiella pneumonia* (altogether 9.7%).

In another original retrospective study done at a tertiary care hospital in Pakistan specifically for SP positive cultures, two years' medical data was traced and reviewed.⁴ Study sample size was 16785, out of which a dismal 48 cases (0.7%) of SP were identified all of which were susceptible to beta lactamases and macrolides but showed resistance against quinolones in 22.5% of the cases. However, this study had a number of limitations. It was a retrospective study from a single centre which had a very low isolation rate. Among the patients found to be culture positive for SP, the age variation was high. Ranging from 2 months to 75 years of age, 42% of the patients were less than 16 years of age. Also, all the patients in this study required hospitalizations and had possible comorbidities. Keeping the above limitations in mind, the conclusions from the study may not particularly apply to the entire population.

A one year cross sectional study based on a pre-designed questionnaire to assess their demographic profiles was conducted at a tertiary care centre in Bahawalpur over a years' time on 160 hospitalized mild-moderate CAP patients.⁵ In contrast to most of the studies, CAP was found to be more common in the age group of 20-40 years. The highlight of this article is that the study was conducted in rural areas of southern Punjab where most of the patients were illiterate and belonged to the lower socio economic class.

A prospective study was conducted at a tertiary care facility to determine the frequency of community acquired respiratory pathogens, specifically paying attention to atypical organisms.⁶ Among 124 patients, an etiologic agent was identified in 52(41.93%). Out of these organisms isolated, 36 were found to be *Mycoplasma* and *Chlamydia pneumoniae*, constituting 69% of the total isolates. The results of the study show an exceptionally high yield for atypicals while a considerably low yield of routine organisms. The forte of this study is the use of serology to identify atypical organisms by which this yield was possible. However the small number of the identified routine organisms (16) does not present a composite picture of etiology of CAP in Pakistan. The study reports that all microbial isolates demonstrated sensitivity to macrolides, with 80% isolates sensitive to fluoroquinolones and 86% sensitive to beta-lactam agents. However, this study does not report individual bacterial sensitivity to various antibiotics.

A two year retrospective study was conducted in three important tertiary care centers in Karachi to record the seasonal incidence of CAP and its mortality in Karachi.⁷ Data relating to 925 patients labelled as CAP on the basis of discharge diagnosis, was collected through respective hospital record departments. Mortality was noted at around 28% in the two- year period. Out of the 905 cases (98%) in which microbial etiology was identified, 500 (54%) had more than one pathogen, the most common being SP followed by *Mycoplasma* and *Chlamydia pneumoniae*. Occurrence of CAP had a seasonal distribution with cases occurring in winter (36%), spring (26%) and summer (20%). Hospitalization trends corresponded with seasonal incidence and were maximum between November and January.

An article describing the efficacy of empirical levofloxacin for hospital admitted patients with CAP, was published online and is a descriptive case series study comprising of 300 cases admitted over a period of six months at a teaching hospital in Lahore.⁸ Therapy included seven days of injectable drug at a dose of 500mg daily. The clinical response was reported to be 67% by which the authors

conclude that levofloxacin as a monotherapy shows improved clinical outcome and patient survival, and had a lower mortality rate, lower treatment failure and lower hospital cost. The study only assessed resolution of clinical symptoms in a fixed seven day time period. It, however, did not report any microbiological or radiological response to correlate with the clinical assessment. The majority of cases were more than forty years of age and the study did not classify smoking status to distinguish clearly whether it was CAP or an acute exacerbation of chronic obstructive pulmonary disease.

Another retrospective study was done at a tertiary care centre from March 2002 till December 2008 to identify etiology and prognosis of severe community acquired pneumonia (SCAP) in adults in accordance with ATS guidelines 2001.⁹ Out of 832 CAP patients, 189(22.7%) were identified as SCAP with 179 requiring ICU care and 10 were managed in the ward. Among the blood and respiratory specimens sent for cultures, microbial etiology was identified in only 47(25%) patients hence demonstrating a low diagnostic yield. The authors have attributed this to non-availability of serologic tests for viruses, or atypical organisms such as *Mycoplasma* and *Chlamydia pneumoniae* which may have been true at the time the study was conducted. However, the time lag of five years for completion of the study renders it less relevant as demonstrated by another study conducted at the same centre and included in our review? Among the identified pathogens, *Staphylococcus aureus* was most commonly found (n=15, 8%), followed by SP (n=14, 7%) and *Pseudomonas aeruginosa* (n=9, 5%).⁹ The mortality rate in this study was calculated at 51% with shock, cardiac arrhythmias and respiratory failure being major causes of death. Due to the retrospective nature of the study, Pneumonia Severity Index (PSI) could not be calculated; instead Acute Physiology and Chronic Health Evaluation (APACHE) II score was used to assess the outcome of the patients. Risk factors found to have a strong association with high mortality included development of septic shock, APACHE II score of >20, BUN > 30mg/dl and a haematocrit <30%.

A non institutional laboratory based study, reviewed sputum samples collected over a period of one year, from its branches catering to different areas of Karachi.¹⁰ The study aimed at determining the prevalence of *Moraxella catarrhalis* and the effectiveness of several antibiotics against it in lower respiratory tract infections (LRTIs). Out of a total sample size of 776, SP was the most frequently identified, followed by *Klebsiella pneumoniae*, *Staphylococcus aureus*, *Pseudomonas*, *E.coli* and *Moraxella catarrhalis* in that order. *Moraxella catarrhalis*

was isolated in 39 out of 776 specimens (5.02%) which showed a high sensitivity to amoxicillin-clavulanic acid, cefotaxime and ceftriaxone (all 100%) and amikacin (92%) while maximum resistance was seen to co-trimoxazole (90%) and doxycycline (76.9%). The study reported a sensitivity of quinolones against *Moraxella catarrhalis* - moxifloxacin 41%, ciprofloxacin and sparfloxacin 33% and ofloxacin 30%. These figures when compared to earlier studies^{1,11} reflect a rapidly rising resistance of *Moraxella catarrhalis* against quinolones within the span of a decade. However, this data specifically focuses on *Moraxella catarrhalis* in the lower respiratory tract and may not necessarily apply to CAP as a whole *Moraxella catarrhalis*.

Pakistan Chest Society (PCS) guidelines is a document first presented by the pneumonia guideline committee of PCS, published for dissemination in 2010.¹² Taking into consideration the most commonly identified local etiologies of CAP; PCS has classified treatment based on British Thoracic Society and American Thoracic Society recommendations.

The guidelines recommend empirical antibiotic treatment with amoxicillin or a macrolide for outpatients in case of first use of antibiotic. In the presence of co-morbidities, two choices have been suggested, a respiratory fluoroquinolone alone, or a beta lactam plus a macrolide. For in patients not requiring ICU, treatment suggested is a respiratory fluoroquinolone (like levofloxacin 750mg OD or moxifloxacin 400mg OD), or a beta lactam plus macrolide. For in-patients requiring ICU, a beta lactam plus either clarithromycin or a respiratory fluoroquinolone is recommended. If there are special concerns about *Pseudomonas*, the beta lactam would require the addition of an aminoglycoside or fluoroquinolone. The alternative to the above combination would be an antimicrobial with anti-pneumococcal and anti pseudomonal activity such as piperacillin/tazobactam, cefipime, imipenem or meropenem, plus either ciprofloxacin or levofloxacin. If Methicillin Resistant *Staphylococcus Aureus* is a consideration, vancomycin or linezolid should be added.

The guidelines state that the emergence of drug resistant pneumococci is well documented but the incidence of resistance appears to have stabilized or may even be decreasing, while data exists that resistance to macrolides and older fluoroquinolones may be increasing. It is to be noted that these are presumptions with no current data available other than what has been reviewed here.

To summarize the results, except for a laboratory based study, no study was published in the first five years beginning 2003. Rest of the publications are datelined

2008 onwards which shows that trend of studying CAP has increased over time. However, it is noteworthy that most of these researches have a time lag between study time period and year of publication, ranging from 0.8 to 4.4 years and they would have been more meaningful were they published in time (See Table: Summary of published literature on CAP 2003-2013).

Among the ten studies, two are purely clinical and have not included any microbiological data. Those that have presented antimicrobial sensitivities, are mainly organism oriented (three studies directed at a single organism,^{1,4,10} one study on two organisms² and one important study focusing mainly on atypical organisms⁶). All of the conducted studies are observational and mainly retrospective, with only two claiming to be prospective. Yet, no studies are available as a follow-up to them that shall help us identify ongoing trends in the antibiotic susceptibilities and resistances of pathogens and CAP related mortality in hospitalized patients. Of the studies available for review, majority (6 out of 9) have been conducted in Karachi with four out of the six being carried out at a single centre alone.

Despite the differences between the studies reviewed, in terms of sample size, location, study population and study design that render the data incomparable, we are obliged to draw conclusions from them, regarding the etiologies and susceptibilities of prevalent microbes causing CAP in Pakistani adults given that this is the only data we have available. In mild to moderate CAP, SP continues to be the most common etiology followed by HI and Klebsiella pneumoniae among the typical pathogens. With the availability of serological tests to identify atypical organisms, it is notable that Mycoplasma and Chlamydia pneumoniae form significant part of the etiology of mild to moderate CAP. With respect to severe CAP, SP, Pseudomonas, Staphylococcus aureus and Acinetobacter, in that order are the predominant etiologies. In contrast, a

single centre study has identified Staphylococcus aureus as the most commonly occurring organism in SCAP patients; however evidence in the form of further studies from multiple centers will be required to be able to apply this finding to the general population.

With respect to mortality, significant variation is present in the figures as shown by the reviewed studies. Mortality is directly proportional to the severity of the disease with up to 51% mortality noted in SCAP patients. Recent studies when compared to older ones show a higher number of deaths hence indicating a rising trend in the mortality associated with CAP in hospitalized patients.

Current data on the antimicrobial susceptibilities and resistances is insufficient and calls for more elaborate studies to be conducted including testing for atypical organisms. PCS guidelines are not purely based on local data, yet, to date, these guidelines remain the most comprehensive document available to guide empirical therapy in patients of CAP in Pakistan. The hallmark of the treatment of CAP as per PCS guidelines is the use of newer fluoroquinolones in almost all cases of CAP. Newer fluoroquinolones such as levofloxacin have concentration dependant activity against bacteria thus allowing for one time administration daily. This ensures patient compliance while minimizing the side effects of the drug. Responsibility and care must be taken to avoid the development of microbial resistances in the general population against efficacious drugs such as levofloxacin.

In order to reduce the morbidity and mortality in adults resulting from CAP in Pakistan, prompt and effective treatment as well as prevention of disease is required. With the approval of pneumococcal vaccine for adults and its availability in Pakistan, and given that SP remains the most common organism causing CAP in adults, it may be of interest to study the efficacy of this vaccine in reducing the morbidity and mortality of pneumonia.

Table: Summary of published literature on CAP from 2003-2013.

S No.	Year of publication	Time period of study	Centre/ city	Microbiology/culture	Antimicrobial sensitivities tested
1	2005	June 2002- Dec 2003	CMH,Rawalpindi	yes	yes
2	2008	2006	AKUH,Karachi	yes	yes-organism specific
3	2009	Jan 2002- Aug 2003	AKUH,Karachi	yes	no
4	2011	Aug 2008- May 2010	PNS Shifa, Islamabad	yes	yes- organism specific
5	2012	Mar 2009- March 2010	Bahawal Victoria Hospital, Bahawalpur	no	no
6	2012	Feb 2007- Mar 2008	AKUH,Karachi	yes	yes- individual sensitivities not reported
7	2012	Jan 2010 - Dec 2011	JPMC, AKUH, LNH Karachi	yes	no
8	2012	6 months	Services Hospital, Lahore	no	no
9	2013	Mar 2002-Dec 2008	AKUH,Karachi	yes	no
10	2013	Oct 2010-2011	Dr.Essa's Diagnostic Lab, Karachi	yes	yes- organism specific

Conclusion

There are indeed significant gaps in the literature available regarding CAP in Pakistan. This warrants the need to conduct more comprehensive studies and present current data to update CAP treatment guidelines for adults in Pakistan.

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