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Community acquired pneumonia-current scenario among immunocompromised patients in a tertiary care hospital

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Abstract: Pneumonia is a common illness accounting for majority of hospitalizations worldwide with significant mortality and morbidity. Antimicrobial therapy, being the main stay of treatment, the choices of antibiotics depends on the nature of the etiologic agents and the host factors. The current study was aimed to identify the bacterial & fungal etiologic agents of Community Acquired Pneumonia (CAP) in Immunocompromised (IC) patients, with their antimicrobial resistant pattern and to analyze the associated immunocompromised states. Various respiratory samples from study group of 75 immunocompromised patients with features of pneumonia were collected, processed and the isolates were identified with their antimicrobial susceptibility& resistance pattern according to CLSI guidelines. The results were analyzed statistically. Diabetes mellitus is the most common immunocompromised state (48%) associated with CAP. Monomicrobial and polymicrobial infection rates were 80.36% and 19.64% respectively. Gram negative pathogens and fungal pathogens were identified in 60% and 25.37% of culture positive cases respectively. Diabetes mellitus is commonly found in association with polymicrobial infection (19.44%) and fungal infection (16.66%). Drug resistant strains comprise about 75% of MRSA strains, 72.72 % of ESBL producers and 3.44% of Amp C producers. As the number of elderly people with associated IC state is on rise, with change in the pattern of microbial etiologic agents causing CAP, a prior knowledge of the host and microbial factors will help in formulating empirical antimicrobial therapy and proper treatment thereby curbing the spread of infections by drug resistant pathogens and the associated morbidity and mortality.

Key words: Community acquired pneumonia; immunocompromised state; drug resistance.

Introduction

Pneumonia is a common illness affecting approximately 450 million people a year and resulting in 4 million deaths. Worldwide >600, 000 individuals hospitalize every year due to pneumonia with annual deaths of 45, 000. Pneumonia in adults is estimated to be prevalent in about 4% of the Indian population with significant mortality and morbidity. Community Acquired Pneumonia (CAP) may be severe enough in about 10% of cases requiring intensive care with mortality rate ranges from 20% to 53%. Also there is rapid emergence of multidrug resistance pathogens causing CAP which contributes to seriousness of these infections. Pneumonia occurring in healthy persons, not confined to an institution, is referred to as Community Acquired Pneumonia. CAP can occur in both Immunocompetent (IP) and immunocompromised(IC) individuals. Immunocompromised host are those who are susceptible to infections by organisms of little virulence in normal individuals, due to their weakened immune system. Although pneumonia can occur in anyone, it occurs with increased frequency and severity in individuals whose immune systems are deficient. Regardless of the reason for altered immune function, pneumonia carries a high mortality in IC patients. With concerns regarding increasing bacterial resistance, antibiotic overuse and immunosuppressive states, therapy should always follow proper diagnosis of pneumonia with identification of etiologic agent and with an idea of their antimicrobial susceptibility and resistant pattern.

This study was conducted over a period of one year in a tertiary care hospital to isolate, identify and to study the antimicrobial resistance patterns of bacterial & fungal agents causing community acquired pneumonia in immunocompromised patients and to study the association of immunocompromised states which predispose to CAP in IC patients.

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Materials and Methods

The study was carried out in a tertiary care hospital, over a period of one year after obtaining Ethical clearance. Those patients above 18 yrs, who are admitted in various wards with presenting signs & symptoms suggestive of pneumonia along with associated immunocompromised state were included in the study. Various respiratory samples like sputum, bronchial wash, BAL fluid, cavity material from lungs and pleural effusion fluid were collected aseptically and were processed immediately in the microbiology department.

Sputum samples were homogenised using sterile glass beads. Only those sputum samples which met the acceptance criteria using Bartlett and Murray's scoring system alone were further processed. Bronchial wash, BAL and pleural fluid were centrifuged and deposit was used for further processing. Cavity material was crushed into small pieces using blunt end of sterile blade and processed further. Direct microscopy was performed by 10% potassium hydroxide mount, Gram's stain and Gomori's Methenamine Silver stain examination.

The sample material was inoculated into MacConkey agar, Blood agar, Chocolate agar and incubated at 37^0C overnight. Also the sample material was inoculated onto two Sabouraud's Dextrose Agar slopes, one incubated at 37^0C and other at 25^0C, to identify the fungal pathogens and incubated up to one month with regular observation.

The isolates were identified by standard methods. Antimicrobial susceptibility pattern for bacterial isolates were tested by Kirby Bauer disc diffusion technique and for fungal isolates by micro broth dilution technique, according to CLSI guidelines and results were statistically analyzed.

Results

During the study period over 75 immunocompromised patients were presented with signs & symptoms of pneumonia, majority of them being males (69. 33%).Commonest age group affected were in the range of 51-70 yrs (47.99%). Diabetes mellitus is the most common immunocompromised state associated with CAP (48%) followed by haematological malignancies (18.66%) (**Chart 1)**. Out of 75 processed samples, culture positivity rate was 74.6%. Monomicrobial infection rate was about 80.36% and polymicrobial infection rate was about 19.64% (**Table 1)**. Gram negative pathogens were predominantly identified in 60% of culture positive cases. The most common isolate was *Klebsiella pneumoniae* (26.86%), followed by *Staphylococcus aureus* (17.91%). Fungal isolates accounts for about 25.37%, *Aspergillus fumigatus* being the most common isolate (52. 94%). *P. jirovecii* was isolated from a retroviral disease patient whose CD4 count was 34 cells/mm^3 **(Table 2)**.

Table 1: Distribution of culture positivity according to the type and combination of pathogens (n=56)

Types & combinations of pathogen isolated		Culture positive		Total no of isolates
		No.	%	
Monomicrobial	Bacterial	30	53.57	30
	Fungal	15	26.79	15
Polymicrobial	Bacterial & Bacterial	9	16.07	18
	Bacterial & Fungal	2	3.57	4
Total		56	100	67

Table 2: Etiologic isolates of community acquired pneumonia in IC patients

S.no.	Bacterial Isolates (n= 67)	No.	%
1.	*Staphylococcus aureus*	12	17.91
2.	*Streptococcus pneumoniae*	8	11.94
3.	*Moraxella catarrhalis*	1	1.49
4.	*Escherichia coli*	1	1.49
5.	*Klebsiella pneumoniae*	18	26.86
6.	*Klebsiella oxytoca*	2	2.98
7.	*Citrobacter koseri*	1	1.49
8.	*Pseudomonas aeruginosa*	5	7.46
9.	*Acinetobacter baumanii*	2	2.98
10.	Fungi	17	25.37

S.no.	Fungal Isolates (n=17)	No.	%
1.	*A. fumigatus*	9	52.94
2.	*A. flavus*	4	23.52
3.	*A. terreus*	3	17.64
4.	*P. jirovecii*	1	5.88

Chart 1: Distribution of associated immunocompromised states (n=75)

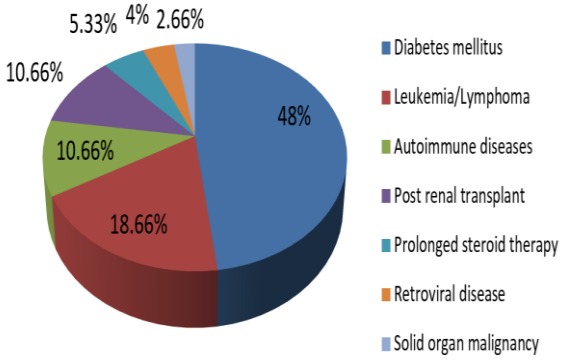
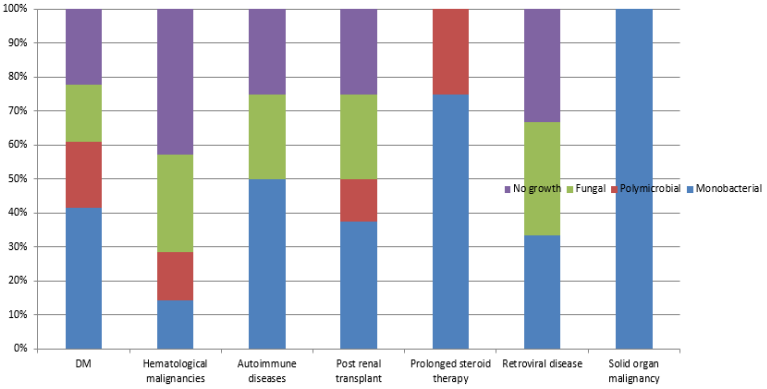
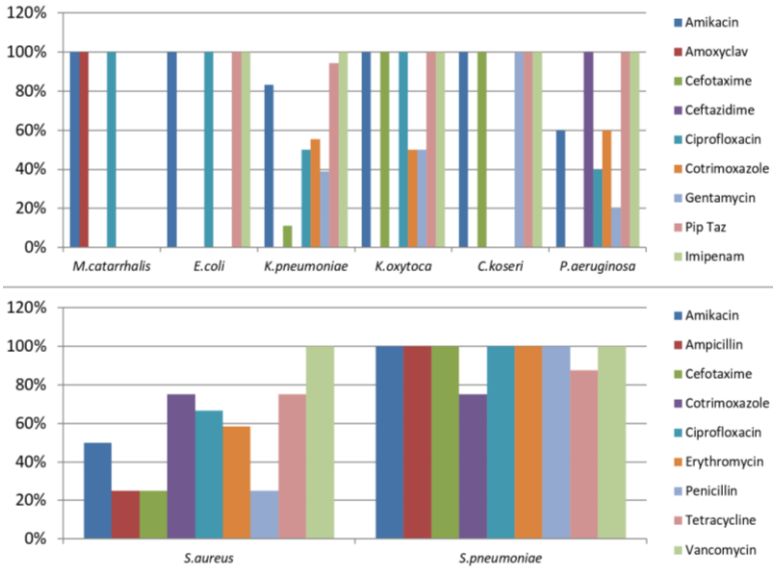


Chart 2: Correlation of immunocompromised state with types of isolates from respiratory samples



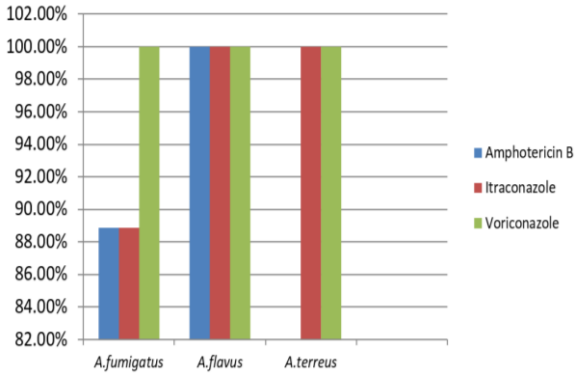
Diabetes mellitus state is commonly found in association with polymicrobial infection (19.44%) and fungal infection (16. 66%). Hematologic malignancies are more commonly associated with fungal infection (28. 57%) **(Chart 2**). The most common bacterial isolate identified in all immunocompromised state was *K. pneumoniae.*

Chart 3: Antimicrobial susceptibility pattern of Gram negative & Gram positive isolates



All Gram positive isolates were 100% sensitive to vancomycin and all *S. pneumoniae* isolates were sensitive to Penicillin. All Gram negative isolates were sensitive to Imipenem (**Chart 3**). It is also evident that 75% of *S. aureus* isolates were MRSA strains and 25% of Pneumococci isolates were Drug Resistant *Streptococcus pneumoniae* (DRSP). 72.72 % of Gram negative isolates were ESBL producers and 3.44% of isolates being Amp C producers. 68.18% and 3.44% of *K. pneumoniae* isolates were ESBL and Amp C producers respectively.4.54% of *E. coli* isolates were ESBL producers.

Chart 4: Antifungal susceptibility pattern



All the *A. terreus* isolates showed 100 % resistance to Amphotericin B, as they are intrinsically resistant and 11.12% of *A. fumigatus* isolates were resistant to Amphotericin B & Itraconazole **(Chart 4)**.

Discussion

Community-acquired pneumonia (CAP) is a common and potentially-serious illness worldwide. It was the eighth-leading cause of death and was responsible for 7% of all deaths both in the United States and in Europe [1]. It occurs about five times more frequently in the developing world versus the developed world [2]. Incidence was almost three-fold higher among immunocompromised patients (30.9 per 1000) than among immunocompetent subjects (11.6 per 1000) [3].

Males (69.33%) are more frequently affected than their female counterparts, owing to risk factors like, smoking, alcoholism, occupation associated development of COPD and congestive cardiac failure. Majority of the patients in the study population are in the age group of 51-70 yrs (47.99%), which might be due to physiologic immune changes, changes in the architecture of lungs and high incidence of chronic diseases in these groups. This results in treatment with medications like steroids, chemotherapeutic agents which results in further immunosuppression.

Diabetes mellitus (48%) was found to be the most commonly associated IC state in patients with CAP due to abnormalities in immune function and associated hyperglycemia, predisposing to infections with a variety of microbial agents. Study conducted by Lyudmila Boyanova *et al.,* [4] observed that DM patients had 1.32-fold higher risk for contracting pneumonia than control group.

Etiological diagnosis was obtained in 56 cases (74.6%) of which pure bacterial growth was obtained in 53.57% which correlates with various studies, which quote that bacteria were the commonest etiologic agents of pneumonia (>50 %). Pure monomicrobial fungal growth was identified in 15 cases (26.79%) and of the total etiologic isolates identified, fungal agents comprised 25.37% (17 isolates). Study conducted by Manahil M *et al.,* [5] in 2012, found that the risk of opportunistic respiratory fungal infections was 2-3 fold higher in IC than in IP patients (60.9% & 39.1% respectively). Similar studies conducted by Chang GC *et al.,* [6] and Pound MW *et al.,* [7] also showed that patients with weakened immune system have a higher chance of acquiring fungal pneumonias.

In our study, 11 cases (19.64%) of polymicrobial infection were identified, in which mixed bacterial pathogens were noted in 9 cases (16.07%) and mixed bacterial and fungal pathogens were identified in 2 cases (3.57%). Study conducted by Gutierrez F *et al.,* [8] showed that polymicrobial infections are more common in patients with underlying immunosuppressed medical condition than in IP patients. Also study conducted by Chang GeeChen *et al.,* [9] showed that bacterial & bacterial mixed pathogens are common type of mixed infections, with bacterial & fungal mixed pathogen being common in IC patients when compared to IP patient, accounting for about 20 % in his study which is higher when compared to our study. Of the 50 bacterial pathogens isolated, gram negative isolates (60%) predominates over gram positive isolates (40%), with no statistical significance. However, study conducted by Helle Leesik *et al.,* [10] on CAP identified gram negative pathogens to be predominantly higher in IC group.

Of the bacterial isolates *Klebsiella pneumoniae* was the most common isolate (26.86%) followed by *Staphylococcus aureus* (17. 91%). Only 11.94% of isolates were found to be *Streptococcus pneumoniae*. Study conducted by Kamat SR *et al.,* [11] and Sainani GS *et al.,* [12] in India, showed that there is a changing pattern in the bacteriology of agents causing CAP in adults. They found that *Streptococcus pneumoniae* has now become an uncommon etiologic agent whereas *Staphylococcus aureus, Klebsiella pneumoniae and Pseudomonas aeruginosa* were becoming predominant etiologic agents, as is shown in our study. This possible change in etiologic pattern may be due to advent of newer antibiotics, their indiscriminate usage and awareness in pneumococcal vaccination.

On considering the fungal pathogens, *Aspergillus fumigatus* was the most commonly isolated one (9 cases, 52.94%) followed by *Aspergillus flavus* (4 cases, 23.52%), Aspergillus *terreus* (3 cases, 17.64%) and *Pneumocystis jirovecii* (1 case, 5.88%, HIV positive patient). Study conducted by John H Reynolds *et al.,* [13] in 2012, Spomenka Ljubic *et al.,* [14] and Pfaller MA *et al.,* [15] found that invasive aspergillosis is most common in IC patients than in normal controls and that *Aspergillus fumigatus* was the most common isolate causing invasive aspergillosis, which correlated with our study results. Study by Manahil M*et al.,* [5] showed that prevalence of *Aspergillus* pneumonia in IP patients is 1 % when compared to 4.9% in IC patients. In our study, PCP is

identified in one HIV positive patient whose CD4 count is 34 cells/mm^3. Study conducted by Torres A *et al.,* [16], recorded a prevalence of 11% PCP in immunosuppressed individual. The reduced detection of PCP infection in our study may be due to the implementation of prophylactic cotrimoxazole therapy in high risk group. Regarding PCP, risk of infection is strongly correlated with CD4 count.

On studying the association of IC state with the types of isolates, diabetes mellitus and haematological malignancies are the two major factors associated with significant fungal etiologic pathogen in CAP (16.66% and 28.57% respectively) and have a higher risk of developing polymicrobial infections (19.44% and 14.28 % respectively). Studies conducted by Mulanovich VE *et al.,* [17] and Pagano L *et al.,* [18], on fungal pneumonia in hematological malignancies, showed that these malignancies pose an important threat for developing fungal pneumonia. Study conducted by Corinna Hahn *et al.,* [19] in 2006, showed that the prevalence of fungal pneumonia in hematological patients vary between 2- 40%, depending on their ongoing treatment protocol. Study conducted by Spomenka Ljubic *et al.,* [14] showed that about 20-25 % of pneumonia in diabetes patients are polymicrobial in nature and fungal pneumonias are common in these patients than with control groups.

All the isolates from the study population show higher level of resistance to first line antibiotics and most of the isolates, especially *Klebsiella* species were ESBL (72.72%) and Amp C producers (3. 44%). This data is supported by the study conducted by Marrie TJ *et al.,* [2] who revealed that the antimicrobial resistance exceeds in IC group compared to control groups. This might be due to IC patients being exposed to repeated hospital environment, use of antimicrobial agents for treatment/ prophylaxis and ongoing microbial replication even with antibiotic therapy, thereby providing an environment for resistant clones to emerge. The prevalence of ESBL producing *K. pneumoniae* isolates detected by a multicentric study conducted in India by Hawser SP *et al.,* [20] showed that 70% of *K. pneumoniae* isolates from lower respiratory tract infections were ESBL producers. Study conducted by Yuichiro Shindo *et al.,* [21] had documented that immunosuppression was a independant risk factor for CAP by Drug Resistant Pathogens (DRPs). Our study reveals that 11.11% of *A. fumigatus* isolates were found resistant to Amphotericin B & Itraconazole which correlates with Study conducted by Mayr A *et al.,* [22] which showed that Amphotericin B & Azoles resistance is common in *A. fumigatus* isolates of lower respiratory tract infections.

Conclusion

The number of elderly patients in the community with immunosuppressive conditions has increased progressively over recent decades and antimicrobial therapy is the mainstay of management for community-acquired pneumonia. The choices of treatment are influenced by the likely etiologic agents, local resistance patterns of the pathogens, as well as patient factors. Early and rapid initiation of empirical antimicrobial treatment is critical for achieving a favourable outcome in CAP.

The causative pathogens responsible for the majority of these infections are developing resistance to our current antimicrobial armamentarium, thus narrowing pharmacotherapeutic options and also continually increasing the challenge for appropriate management. An urgent need exists for new agents as well as for thorough surveillance programs to track resistance patterns among respiratory pathogens as the morbidity and mortality associated with the RTIs caused by these pathogens pose a significant and growing challenge to clinical practitioners. Surveillance information will aid the clinician in appropriately targeting treatment in this increasingly difficult health care arena. Proper suspicion upon clinical manifestation, relevant history, microbiology laboratory findings and radio imaging, aid in early diagnosis and help to implement appropriate antibiotic therapy and together with identification and treatment of associated IC conditions, they help to curb the seriousness and spread of these infections. Physicians can predict infection pattern and drug resistance pattern in patients with CAP by taking account of the associated IC states, thereby aiding in proper approach to treatment in these high risk group of people.

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