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Preliminary study of the baseline characteristics of patients, etiological agents of community-acquired pneumonia and mortality in Ibadan, Nigeria.

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Abstract
Background: Studies relating the baseline characteristics of patients with community-acquired pneumonia and the bacterial etiological agents to the mortality of the disease are scanty in our environment. This study therefore aimed at determining the contribution of the baseline characteristics of patients with community-acquired pneumonia, the bacterial etiological agents to the mortality in our environment.

Methods: Data of patients with community-acquired pneumonia were retrieved and the effects of these on mortality were studied retrospectively. These data included age, gender, occupations, marital status, smoking, severity assessment using CURB 65 score, alcohol use, sources of referral, and bacterial etiological agents. These were subjected to statistical analysis using the SPSS version 15.

Results: The age groups with the highest mortality frequencies were those below 30years (41.1%) and above 60years (29.4%). Marital status, gender of patients, use of alcohol and smoking did not seem to affect the mortality rates. Eight patients had concomitant chronic obstructive pulmonary disease and four died (50.0%) while 12 patients had bronchial asthma, none of whom died. Patients with *Pseudomonas aeruginosa* infections had the highest mortality rates (5.9% and 17.6%) in cases of single and multiple pathogens respectively. None of the patients had severity score documented on admission.

Conclusion: This is a preliminary study and further studies are necessary to determine the relationship of smoking, alcohol and etiological agents to mortality in community-acquired pneumonia using a larger population as study size.

Keywords: *Community-acquired pneumonia, mortality, baseline characteristics.*

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Résumé
Introduction : Les études exprimant les caractéristiques de base des patients avec la pneumonie acquise de la communauté et les agents bactériens étiologiques à la mortalité de la maladie sont rare dans notre environnement. C'est pourquoi cette étude visa à déterminer la contribution des caractéristiques de base des patients avec la pneumonie acquise de la communauté, les agents bactériens étiologiques à la mortalité dans notre environnement.

Méthode : Les données des patients avec la pneumonie acquise de la communauté étaient recouvrées et les effets de celles-ci sur la mortalité étaient étudiés rétrospectivement. Ces données comprenaient l'âge, gendre, occupations, position maritale, l'habitude de fumer, sévérité de répartition en utilisant 65 scores CURB, usage d'alcool, sources de renvoi, et agents bactériens étiologiques. Ceux-ci étaient assujettis à l'analyse statistique en utilisant la version 15 d'SPSS.

Résultats : Les groupes d'âges avec les plus hautes fréquences de mortalité étaient ceux au-dessous de 30 ans (41,1%) et au-delà de 60 ans (29,4%). La position maritale, gendre des patients, usage d'alcool et habitude de fumer ne s'emblaient pas affecter les taux de mortalité. Huit patients avaient une concomitante maladie pulmonaire obstructive chronique et quatre moururent (50,0%) tandis que 12 patients avaient l'asthme bronchial, aucun desquels mourut. Les patients avec les infections de *Pseudomonas aeruginosa* avaient les plus grands taux de mortalité (5,9% et 17,6%) dans les cas de pathogènes simple et multiple respectivement. Aucun des patients n'avait le score de sévérité documenté à l'admission.

Conclusion : Ceci est une étude préliminaire et des études ultérieures sont nécessaires à déterminer le rapport de l'habitude de fumer, alcool et agents étiologiques à la mortalité dans la pneumonie acquise de la communauté en utilisant une population plus large comme grandeur d'étude.

Mots clé: *Pneumonie acquise de la communauté, mortalité, caractéristiques de base*

Introduction
Various studies have reported Community-acquired pneumonia (CAP) as a common cause of hospitalization and mortality both in the developed and the developing parts of the world [1-3].

Mortality rates of 8.1 %, 9.1 %, 22.7%, and 26% have been reported by workers in Canada, United States of America, Nigeria and Spain respectively [2-5]. Mortality in hospitalized CAP patients seems to remain high despite the availability of potent antibiotics. Pobee reported a mortality rate of 13.5% in Ghana [6], Riquelme, 26% in Spain [2], 11.9% at Enugu [7] in Nigeria and 15% also in Enugu [8] in Nigeria.

This may be attributable to the severity of the disease, delay in initiation of therapy, advanced age or co-morbidities at presentation [9-12].

There have been very few studies relating the socio-demographic characteristics of patients and the etiological agents of CAP to the mortality rate despite the high mortality associated with the disease. This retrospective study was therefore conducted to relate some of the baseline characteristics of patients, the bacterial pathogens of CAP to their effects on the mortality using the clinical history obtained from patients admitted with the disease in the clinical wards of University College Hospital, Ibadan, Nigeria.

Materials and methods
This study was conducted at the University College Hospital, a tertiary instituition in Ibadan, Nigeria, between January 2010 and December 2012.

The case notes of all patients admitted for CAP to the medical wards during the study period were retrieved and reviewed. The diagnosis of CAP was made when a patient presented with 2 or more acute symptoms or signs of the disease. These included cough (productive or non-productive), dyspnoea, fever (temperature $\geq 38^{\circ}$C), pleuritic chest pain, crackles, or bronchial breathing on auscultation of the chest, and evidence of lobar consolidation in chest x-ray as interpreted by the consultant radiologist.

Data relating to their age (years), gender, occupation, marital status, history of smoking and alcohol use, concomitant COPD or asthma, sources of referral, laboratory results indicating etiological agents and their susceptibility patterns, antibiotics prescribed and used, and severity assessment using CURB 65 score, were extracted for statistical analysis. The outcome of the disease was obtained from the end of treatment case file summary and classified as either discharged or died.

Statistical analysis
All the data were analyzed using the statistical software SPSS version 15 (SPSS Inc, Chicago IL).

The results were expressed as frequencies, percentages and range. Quantitative continuous variables were compared using Student's t test, categorical variables were compared using the chi-square test or Fisher's exact test where appropriate. p-value of 0.05 or less was regarded as significant.

Results
Two hundred and sixty (260) patients were admitted for CAP at this study period. There were 148 (56.9%) males and 112 (43.1%) females and gender was found to have no effect on the mortality due to CAP ($P=0.440$) (table1). None of the patients had severity score documented on admission.

Out of the 260 patients admitted, 192 (73.8%) were discharged and 68 (26.2%) died. The highest frequency of deaths occurred in the 21-30 years (23.5%) and 61-70 years (23.5%) age-groups. The history of smoking among the patients showed that 24 (9.2%) patients were current smokers, out of whom 4 (16.7%) died. Two hundred and twenty-eight (87.7%) patients had never smoked and the mortality rate in them was 60 (26.3%). The smoking status therefore had no effect on mortality (P=0.874) in this study.

Of the 260 participants, 52(20%) were current alcohol users and 48 of these were discharged which was 92.3% survival. Of the 208 who never used alcohol, 64 (30.8%) died.
Out of 168 married patients with CAP, 48 (28.6%) died, while out of the 76 single patients, 20 (26.3%) died. The 12 widowed and 4 divorced were all discharged. The marital status therefore had no significant effect on the mortality (p= 0.231) (Table1).

Table 2 shows the CAP patients with concomitant chronic obstructive pulmonary disease (COPD) or asthma and the antibiotics prescribed. Eight patients had COPD and 4 (50%) died, while 12 patients had bronchial asthma but none died (100% survival). Beta- lactam antibiotics and metronidazole were used to treat 160 (61.5%) of the patients, while 30.8% and 5.3% of them were treated with a β-lactam with and without macrolides respectively and a few with fluoroquinolones (2.3%.).

In the percentage distribution of the CAP patients with regards to occupation, the most common occupation among the patients was trading 76 (29.2%), followed by schooling 52 (20.0%). Others in order of frequency were civil servants, 36 (13.8%), farmers, 32 (12.3%),

Table 1: Socio-Demographic Characteristics of patients with community-acquired pneumonia.

Characteristics	Discharged No (%)	Died No (%)	Total No (%)	Chi²	P value
Age					
11-20	32 (16.7)	12 (17.6)	44 (16.9)		
21-30	48 (25)	16 (23.5)	64 (24.6)		
31-40	24 (12.5)	8 (11.8)	32 (12.3)	18.307	0.006
41-50	24 (12.5)	4 (5.9)	28 (10.8)		
51-60	40 (20.8)	8 (11.8)	48 (18.5)		
61-70	12 (6.3)	16 (23.5)	28 (10.8)		
70+	12 (6)	4 (5.9)	16 (6.2)		
Sex					
Male	112 (58.3)	36 (52.9)	148 (56.9)	0.595	0.440
Female	80 (41.7)	32 (47.1)	112 (43.1)		
Marital Status					
Married	120 (62.5)	48 (70.6)	168 (64.6)		
Single	56 (29.2)	20 (29.4)	76 (29.2)	1.437	0.231
Widowed	12 (6.3)	-	12 (4.6)		
Divorced	4 (2)	-	4 (1.5)		
Smoking History					
Never	168 (87.5)	60 (88.2)	228 (87.7)	0.025	0.874
Past	4 (2.1)	4 (5.9)	8 (3.1)		
Current	20 (10.4)	4 (5.9)	24 (9.2)		
Alcohol Use					
No	144 (75)	64 (94.1)	208 (80.0)	11.471	0.01
Yes	48 (25)	4 (5.9)	52 (20.0		

Table 2: Concomitant COPD/Asthma, and antibiotic treatment prescribed

Characteristics	Discharged No (%)	Died No (%)	Total No (%)	X²	P value
Concomitant COPD or Asthma					
Yes					
COPD	4 (2.1)	4 (5.9)	8 (3.1)		
ASTHMA	12 (6.3)	Nil (0.0)	12 (4.6)	0.425	0.515
No	176 (91.7)	64 (94.1)	240 (92.3)		
Antibiotic treatment prescribed					
β lactam + Metronidazole	115 (59.9)	45 (66.2)	160 (61.5)		
β- lactam + macrolide	65 (33.9)	15 (22.1)	80 (30.8)	55.629	0.01
β lactam alone	8 (4.2)	6 (8.8)	14 (5.3)		
Fluroquinolone alone	4 (2.1)	2 (2.9)	6 (2.3)		

artisans, 24 (9.2%), and retirees, 16 (6.2%) (Figure1).Out of the 76 traders, 32 (42.1%) died, and, out of 52 schooling,12 (23.1%) died. Eight patients (50%) died among the retirees and 8 (22.2%) among the civil servants. Four (12.5%) deaths occurred among the farmers, and 4 (16.7%), among the artisans.

The percentage distribution of the CAP patients with regards to the sources of referral shows that 192 (73.8%) were from the accident and emergency unit of our hospital, while 44(17.0%) accounted for those from private hospitals and clinics. Referrals from other departments of the hospital were 12 (4.6%), while medical out-patient,
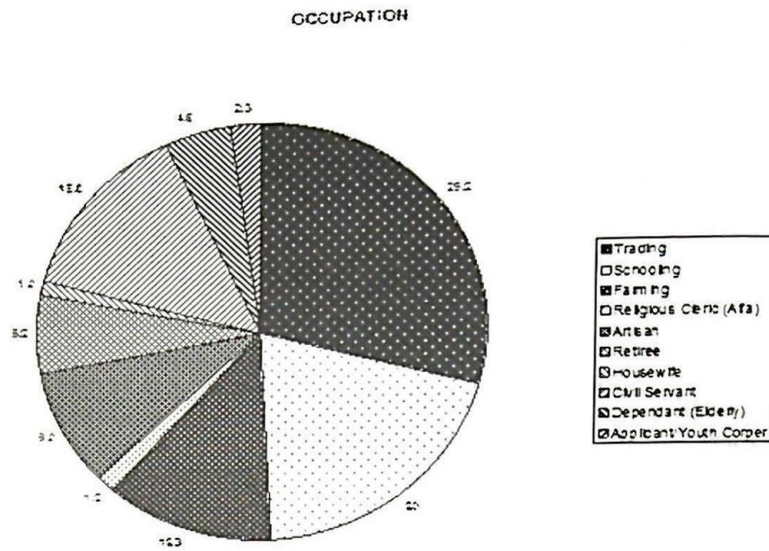
OCCUPATION

Fig. 1: Percentage distribution of the CAP patients with regards to the occupations.
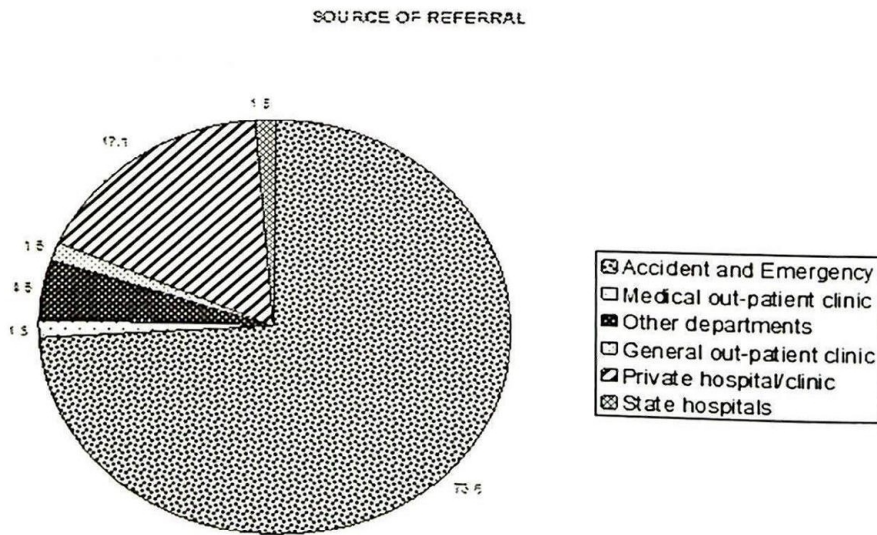
SOURCE OF REFERRAL

Fig. 2: Percentage distribution of the CAP patients with regards to the sources of referral.

general out- patient clinics and state hospitals accounted for the rest of the referrals (Fig.2).

The source of referral did not seem to affect the treatment outcome because the mortality rate of 52/192(27.0%) was recorded from the referrals from the accident and emergency unit while that from the hospitals and clinics outside our institution accounted for 12/44(27.3%).

The etiological agents and mortality of the 260 cases of CAP is as shown in table 3. Patients with *Pseudomonas aeruginosa* infections had higher fatality rate of 5.9% among cases with single pathogens and 17.6% among cases with multiple pathogens.

Table 3: Etiological agents in relation to mortality in 260 cases with CAP

Etiological agents	Cases		Fatal cases	
	n (260)	% (100)	n (68)	% (26.2)
Single Pathogens				
Streptococcus pneumoniae	26	10	2	2.9
Klebsiella species	64	24.6	3	4.4
Pseudomonas aeruginosa	30	11.5	4	5.9
Escherichia coli	14	5.4	3	4.4
Haemophilus influenzae	27	10.4	2	2.9
Staphylococcus aureus	9	3.5	3	4.4
Streptococcus pyogenes	6	2.3	3	4.4
Multiple pathogens				
Klebsiella species + *E. coli*	4	1.5	5	7.4
Klebsiella species +				
Pseudomonas aeruginosa	7	2.6	12	17.6
Klebsiella + Proteus species	5	1.9	6	8.8
Staphylococcus aureus +				
H. influenzae	4	1.5	8	11.8
Klebsiella species + *H. influenzae*	4	1.5	9	13.2
Etiology unknown	60	23.1	8	11.8

Discussion

In this study, the mortality rate of hospitalized patients with CAP was 26.2%. This is high despite the use of potent antibiotics at that period, however, this is comparable with the study of Sofowora and Onadeko who reported a mortality rate of 22.7% in a previous study conducted in the same environment [3] .

The highest mortality occurred in the 21-30 years and the 61-70 years age groups, and accounted for 23.5% each. This is in contrast to previous studies which showed that the elderly with CAP had more severe disease, and hence higher mortality than the younger ones [7,9,15,16].

The male to female ratio of 1.3: 1.0 obtained in this study, was in keeping with the results of the study by Sofowora and Onadeko which also did not show any significant male preponderance in the prevalence of the disease [3]. Some African studies, however, have documented the male to female ratio to be as high as 3.6:1 and 4:1, showing significant male preponderance, but all, including this study, agreed that gender has no effect on the mortality rate of patients with CAP [6,10].

As regards occupation, the highest mortality was found among retirees (50%), followed by traders (42.1%), schooling (23.1%), civil servants (22.2%), artisans (16.7%) and farmers (12.5%). Approximately equal proportions of patients died from the married and the single groups and there was no significant difference in the marital status of the participants and mortality (*P*=0.23).

In this study, the smoking status was found to have no significant effect on the mortality due to CAP (P=0.87). Studies have shown that smokers are more likely to have CAP caused by Legionella spp and *Chlamydia pneumoniae* which are bacterial pathogens for atypical pneumonia [17]. Moreover, smoking has been described as an independent risk factor for sporadic legionellosis [17]. This could not be ascertained in this study as serology to detect the pathogens was not done. The importance of smoking can be seen indirectly as it leads to chronic bronchitis (COPD), and, such patients, have colonization of their airways with *Streptococcus pneumoniae*, *Hemophilus influenzae* and *Moraxella cattarhalis* [18,19].

Smoking is a well known risk factor for respiratory infectious diseases because it changes the respiratory tract's mucosal surface and its function, increasing the number of abnormal cilia and permeability of the airway epithelium [20-22] . These effects impair mucociliary clearance, increase bacterial adherence and airway colonization, and, help infectious organisms enter from the airway into the interstitium and parenchyma of the lungs [23]. Smoking also causes impairment of systemic immune function; smokers are more likely to have reduced helper and suppressor T-cell ratio, natural killer cell activity and immunoglobulin levels

compared with non-smokers [24,25].This study did not show any significant effect of smoking on the mortality due to CAP possibly because most of the patients were light smokers. This contradicts previous studies that showed an increase in the mortality rate from pneumonia in smokers, and that the mortality increased with the amount of cigarettes smoked [26,27].

In this study, 92.3% survival was recorded among the patients who were current alcohol users while the mortality rate among those who had never used alcohol was 30.8%. The study therefore showed that the patients with current alcohol use had no increased risk of death from pneumonia compared with the non-alcohol users. However, heavy alcohol intake has been closely related to the risk of pneumonia and with increased mortality [28-30], but our study had limited power to observe the effect of heavy alcohol drinking, but possibly adequate to determine that there was no association between low or moderate alcohol intake and risk of increased mortality due to CAP.

Chronic obstructive pulmonary disease (COPD) is a frequent co-morbidity in patients hospitalized with CAP and is usually associated with increased mortality [31-33]. The mortality rate of 50% among the patients with COPD in this study was therefore in agreement with this. The results of this study have also indicated better prognosis for patients with bronchial asthma and CAP than patients with COPD and CAP since none of the former died.

As at the time of this study, it was demonstrated that the major single pathogens causing pneumonia in Ibadan, Nigeria, were Klebsiella species (24.6%), *Pseudomonas aeruginosa* (11.5%), *Hemophilus influenzae* (10.4%) and *Streptococcus pneumoniae,* (10.0%) . These observations were different from the findings of Ozylimaz *et al* from Turkey, and Liebowitz *et al* from South Africa, where *Hemophilus influenzae* was the most prevalent single pathogen followed by *Streptococcus pneumoniae* and *Moraxella catarrhalis* [34,35].

The most frequent mixed infection in this study was Klebsiella species and *Pseudomonas aeruginosa* (2.6%) whereas in a study conducted by de Roux *et al*, *Streptococcus pneumoniae* and *Hemophilus influenzae* constituted the most frequent cause of mixed infections [36].

Patients with CAP, who were treated with β-lactam antibiotics and metronidazole, were 61.5%, while 30.8% and 5.3% of them were treated with a β-lactam with or without macrolides respectively and a few with fluoroquinolones (2.3%). The mortality rate among patients treated with β-lactam and metronidazole was 28.1%, 18.8% with β-lactam and macrolide, 42.9% with β-lactam alone and 33.3% with fluoroquinolones alone (p=0.01). This study has therefore demonstrated that there was a significant difference in mortality as regards the antibiotic treatment received. In this study, conducted at a teaching hospital in Nigeria, very potent antibiotics were used, following the guidelines for the management of adults with lower respiratory tract infections [32-38].

In conclusion, this study has highlighted some baseline characteristics of patients as they affect the treatment outcome. There is need for further studies, however, to determine the contribution of factors such as alcohol use and smoking to the mortality of patients admitted for community-acquired pneumonia in Nigeria.

References

1. Macfarlane J. Community-acquired pneumonia. Br J Dis Chest 1987; 81: 116-127.
2. Riquelme R, Torres A, El-Ebiary M, *et al.* Community-acquired pneumonia in the elderly; a multivariate analysis of risk and prognostic factors. Am J Respir Crit Care Med 1996;154:1450-1455.
3. Sofowora EO and Onadeko BO. Complications and prognostic factors in pneumonia; mortality among Nigerians. Nig Med J 1973; 3: 144-145.
4. Marie TJ and Wu L. Factors influencing in-hospital community-acquired pneumonia. Chest 2005; 127: 1260-1270.
5. Arozullah AM, Parada J, Bennett *et al*. A rapid staging system for predicting mortality from HIV-associated community-acquired pneumonia. Chest 2003; 123: 1151-1160.
6. Pobee JOM. Some aspects of pneumonia in Ghanaian Africans. Nig Med J 1983;13 (1):63-67.
7. Cajetan C, Onyedum CC and Chukwuka JC. Admission profile and management of community-acquired pneumonia in Nigeria- 5 year experience in a tertiary hospital. Resp Med 2011;105:298-302.
8. Mbata GC, Chukwuka CJ,Onyedum CC, *et al.* The role of complications of community-acquired pneumonia on the outcome of illness:a prospective observational study in a tertiary institution in Eastern Nigeria. Ann Med Hlth Sci Res 2013;3:365-369.
9. Marrie TJ, Durant H and Yates L. Community-acquired pneumonia requiring hospitalization: 5-year prospective study. Rev Infect Dis 1989; 11:586-599.

10. Mortensen EM, Coley CM, Singer DE, *et al.* Causes of death for patients with community-acquired pneumonia: results from the Pneumonia Patients Outcome Research Team cohort study. Arch Intern Med 2002; 162:1059-1064.

11. Zalacain R, Torres A, Celis R, *et al.* Community-acquired pneumonia in the elderly: Spanish multicentre study. Eur Respir J 2003; 21:294-302.

12. Roson B, Carratala J, Fernandez-Sabe N, *et al.* Causes and factors associated with early failure in hospitalized patients with community-acquired pneumonia. Arch Intern Med 2004; 164:502-508.

13. Menendez R, Torres A, Zalacain R, *et al.* Risk factors of treatment failure in community-acquired pneumonia: implications for disease outcome. Thorax 2004; 59:960-965.

14. Torres A, Dorca J, Zalacain R, *et al.* Community-acquired pneumonia in chronic obstructive pulmonary disease: a Spanish multicentre study. Am J Respir Crit Care Med 1996; 154: 1456-1461.

15. Ruiz M, Ewigg S, Marcos MA, *et al.* Etiology of community-acquired pneumonia: impact of age, comorbidity, and severity. Am J Respir Crit Care Med 1996; 160:397 405.

16. El Solh AA, Brewer T, Okada M, *et al.* Indicators of recurrent hospitalization for pneumonia in the elderly. J Am Geriatr Soc 2004; 52: 2010-2015.

17. Straus WL, Plouffe JF, File TMJ, *et al.* Risk factors for domestic acquisition of legionnaires disease. Arch Intern Med 1996; 156:1685-1692.

18. Almirall J, Bolibar I, Balanzo X and Gonzalez CA. Risk factors for community-acquired pneumonia in adults: a population-based case-control study. Eur Respir J 1999; 13: 349-355.

19. Almirall J, Gonzalez CA, Balanzo X and Bolibar I. Proportion of community-acquired pneumonia cases attributable to tobacco smoking. Chest 1999; 116:375-379.

20. Sherman CB. The health consequences of cigarette smoking. Med Clin North Am. 1992; 76:273-293.

21. Verra F, Escudier E, Lebaroy F *et al.* Ciliary abnormalities in bronchial epithelium smokers, ex-smokers and non-smokers. Am J Respir Crit Care 1995; 1151: 630- 634.

22. Jones JG, Minty BD, Lawler P *et al.* Increased alveolar epithelial permeability in cigarette smokers. Lancet 1980; 11 :66-68.

23. Piatti G, Gazzola T and Allegra L. Bacteria adherence in smokers and non-smokers. Pharmacol Resp. 1997; 36: 481-484.

24. Miller LG, Goldstein G, Murphy M and Ginnus LC. Reversible alterations in immune –

25. Ferson M, Edwards A and Lind A, Milton GW and Hersey P. Low natural killer-cell activity and immunoglobulin levels associated with smoking in human subjects. Int J Cancer 1979; 23: 603-609.

26. Lange P, Vestibo J and Nyboe J. Risk factors for death and hospitalization from pneumonia a prospective study of a general population. Eur Resp J 1995; 8: 1694-1698.

27. Carstensen JM, Pershagen G, Ekland G and Ekhund G. Mortality in relation to cigarette and pipe smoking: 16 years observation of 25,000 Swedish men. J Epidemiol Community Health 1987; 41:166-172.

28. Rogot E and Murray JL. Smoking and causes of death among US veterans: 16 years of observation. Public Health Resp 1980; 95:213-222.

29. Fernandez-Sola J, Jungue A, Estruch R, *et al.* High alcohol intake as a risk and prognostic factor for community-acquired pneumonia. Arch Intern Med 1995; 155: 1649-1654.

30. Baik I, Curhan GC, Rimm EB, *et al.* A prospective study of age and lifestyle factors in relation to Community-Acquired Pneumonia in US men and women. Arch Intern Med. 2000; 160: 3082-3088.

31. de Rouux A, Cavaleanti M, Marcos MA, *et al.* Impact of alcohol abuse in the etiology and severity of community-acquired pneumonia. Chest 2006; 129:1219- 1225.

32. Mandell LA, Wunderink RG, Anzueto A, *et al.* Infectious Diseases Society of America/ American Thoracic Society consensus guidelines on the managment of community-acquired pneumonia in adults. Clin Infect Dis 2007; 44:Suppl. 2, S27-S72.

33. Restrepo MI, Mortensen EM, Pugh JA and Anzueto A. COPD is associated with increased mortality in patients with community-acquired pneumonia. Eur Respir J 2006; 28:346-351.

34. Liapikou A, Polverino E, Ewig S, *et al.* Severity and outcomes of hospitalised community-acquired pneumonia in COPD patients. Eur Respir J 2012;39:855-861.

35. Ozylimaz E, Akan OA, Gulhan M, *et al.* Major bacteria of community-acquired respiratory tract infections in Turkey. Jpn J Infect Dis 2005; 588:50-52.

36. Liebowitz LD, Slabbert M and Huisamen A. National surveillance programme on susceptibility patterns of respiratory pathogens in South Africa: moxifloxacin compared with

eight other antimicrobial agents. J Clin Pathol 2003; 56: 344-347.

37. de Roux A, Ewig S, Carcia E, *et al*. Mixed community-acquired pneumonia in hospitalized patients. Eur Respir J 2006; 27: 795-800.

38. Woodhead M, Blasi F, Ewig S. *et al*. Guidelines for the management of adult lower respiratory tract infections- Full version. European Society of Clinical Microbiology and Infectious Diseases CMI. 2011;17 (Suppl 6): E1- E59.