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# Decrease in Mortality in Severe Community-Acquired Pneumococcal Pneumonia: Impact of Improving Antibiotic Strategies (2000-2013).

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STRUCTURED ABSTRACT

OBJECTIVE: To compare antibiotic prescribing practices and survival in the intensive care unit (ICU) in pneumococcal severe community-acquired pneumonia (SCAP) between 2000 and 2013.

MATERIALS AND METHODS: Matched case-control study of two prospectively recorded cohorts in Europe. Eighty patients from CAPUCI II (cases) were matched with 80 patients from CAPUCI I (controls) based on: shock at admission, need of mechanical ventilation, COPD, immunosuppression and age.

RESULTS: Demographic data were comparable in the two groups. Combined antibiotic therapy increased from 66.2% to 87.5% ($p < 0.01$) and first dose of antibiotic was given within 3 hours from 27.5% to 70% ($p < 0.01$). ICU mortality was significantly lower (OR 0.82, 95%CI 0.68-0.98) in cases, both in the whole population and in the subgroups of patients with shock (OR 0.67, 95%CI 0.50-0.89) or under mechanical ventilation (OR 0.73, 95%CI 0.55-0.96). In the multivariate analysis, ICU mortality increased in patients requiring mechanical ventilation (OR 5.23, 95%CI 1.60-17.17), and decreased in patients receiving early antibiotic treatment (OR 0.36, 95%CI 0.15-0.87) and combined therapy (OR 0.19, 95%CI 0.07-0.51).

CONCLUSIONS: In pneumococcal SCAP, early antibiotic prescription and use of combination therapy increased; both were associated with improved survival.

Abbreviation: ICU, Intensive Care Unit; CAP, Community-Acquired Pneumonia; SCAP, Severe Community-Acquired Pneumonia; IDSA/ATS, Infectious Disease Society of America, American Thoracic Society; COPD, Chronic Obstructive Pulmonary Disease; IQR, Interquartile Range.

INTRODUCTION

Community-acquired pneumonia (CAP) is a major health problem associated with high morbidity and mortality (1,2). Despite geographical differences, *Streptococcus pneumoniae* is the most common cause of pneumonia worldwide (1).

Over the years, CAP's studies have focused on risk factors (3), microbiology (4,5), biomarkers (6,7) and mortality (8); recently, they have been addressed to the introduction of new antibiotic policies and availability of new drugs (9,10).

Despite improved survival due to changes in antibiotic policies (11,12,13), in Western countries poor prognosis is seen in older people with more comorbidities and chronic illness, in whom life expectancy has been prolonged (14,15,16,17). On the other side, it has been shown that septic shock mortality decreased (18,19,20). The aggregate impact of these demographic and clinical trends on the survival of CAP is of great importance to clinicians, but no recent data are available in the literature, especially in critical patients with severe community-acquired pneumonia (SCAP).

Our hypothesis was that improvement in antibiotic policies contributed to reduce mortality due to SCAP in the ICU setting. For this reason, the primary objective of the present study was to compare ICU mortality due to SCAP caused by *Streptococcus pneumoniae* in two different periods (2000-2002 and 2008-2013). The secondary objective was to identify changes in antibiotic strategies in pneumococcal SCAP.

MATERIALS AND METHODS

Matched case-control study of two cohorts of patients prospectively recorded in Europe (CAPUCI studies). CAPUCI I and II are two European prospective multicenter studies conducted in patients admitted to the ICU for CAP. The CAPUCI I study recorded data from 33 hospitals from 2000 to 2002. Data from this cohort have been reported elsewhere (11). The CAPUCI II study was a follow-up project endorsed by the European Critical Care Research Network (ECCRN). Data were recorded from patients admitted for SCAP, between 2008 to 2013, in 29 European ICUs. Demographic data, clinical presentation, outcomes and data on antibiotic therapy were registered; antibiotic prescription was left to the discretion of the attending physician. Patients were admitted to the ICU either to undergo mechanical ventilation or because they were critically ill (21), in accordance to IDSA/ATS guidelines (1). People with severe chronic illness in whom pneumonia was an expected terminal event were not included; patients were observed until ICU discharge or death. The study was approved by the Ethics Board of coordinating center (REF 2005/NA), in accordance with national regulations, and informed consent was waived due to the observational nature of the studies. Definitions have been reported as Electronic Supplementary Material.

Eighty patients (CASE GROUP, n = 80) diagnosed with SCAP caused by *Streptococcus pneumoniae* from the CAPUCI II database were matched with 80 patients from the CAPUCI I (CONTROL GROUP, n = 80), with similar clinical characteristics. For each patient in the case group, one patient with identical clinical features was selected from the control group. Matching variables were: presence of shock at ICU admission, need for mechanical ventilation, immunosuppression and age (age cut-off: 65 years) (22), as these are main determinants for mortality in CAP (23,24), and COPD, given its high prevalence in Western populations and its controversial role in the increase in mortality in SCAP (25,26).

Continuous variables were compared with Student t test for normally distributed variables, or the Mann-Whitney U test for non-normally distributed variables. Categorical variables were evaluated with the chi-square or two-tailed Fisher exact test. Results are expressed as median and interquartile range (IQR) for continuous variables, or as percentages of the group from which they were derived for categorical

variables. Two-tailed tests were used to determine statistical significance; a p value < 0.05 was considered significant.

The Kaplan-Meier product limit method was used to construct survival curves for patients receiving combination and monotherapy regimens and early versus late antibiotic administration. All data management and statistical analysis were performed using the SPSS 15 processor (SPSS Inc., Chicago, IL, USA).

RESULTS

One hundred and sixty patients were enrolled: 80 patients from the 2008-13 cohort (cases) paired with 80 from the 2000-02 cohort (controls). Figure 1 shows the algorithm for the selection of the patients and the ICU mortality for each subgroup; incidence of severe pneumococcal pneumonia increased significantly (43.9% versus 27.0%; OR 1.30, 95%CI 1.15-1.48). Table 1 shows the variables used to match patients. The groups presented identical prevalence of the items evaluated: shock at ICU admission was present in 60.0% of patients, while 65.0% had undergone mechanical ventilation. Thirty-three per cent of patients were aged over 65; 32.2% were diagnosed with COPD and 7.5% presented immunosuppression. The cause of immunosuppression was infection due to Human Immunodeficiency Virus in 7 of 12 patients.

Medical history and clinical presentation were comparable in the two cohorts (table 2). Estimated probability of death was 31.0% in cases and 24.0% in controls (p 0.35); ICU length of stay was similar: median and interquartile range (IQR) were 10.0 (4-19) versus 10.0 (4-17.8) days (p 0.97). Blood cultures were positive in 36.2% of cases and 40.0% of control (p 0.75). As shown in table 3, bacteremia was significantly associated with presence of septic shock (p 0.05). Acute kidney injury was observed in 44 (55.0%) patients in the case group versus 31 (39.2%) in controls (p 0.06), while rapid radiographic spread was recorded in 48.8% and 51.2% respectively (p 0.87).

ICU mortality was significantly different between the groups: 14 (17.5%) patients from the case group died compared with 27 (32.5%) controls, with a OR of ICU mortality of 0.82 (95%CI 0.68 - 0.98), p 0.04. Most deaths were late and due to multiorgan dysfunction syndrome. Figure 1 shows ICU mortality of the different subgroups: mortality was comparable between matched and non-matched patients in CAPUCI I (22.6% versus 33.8%; p 0.26) and in CAPUCI II (17.5% vs. 14.2%, p 1.00).

Figure 2 shows changes in ICU mortality between the two time periods in the whole population and in the subgroups of patients with shock: OR 0.67 (95%CI 0.50-0.89), and under mechanical ventilation: OR 0.73 (95%CI 0.55-0.96).

Kaplan-Meier survival analysis was performed in the global cohort and in the subgroup of patients with shock and under mechanical ventilation, stratifying by monotherapy versus combined therapy (figure 3; log rank p value respectively <0.01, 0.02 and 0.01)

and early versus non-early antibiotic treatment (figure 4; log rank p value <0.01, 0.01 and 0.02).

Combined therapy differed significantly between the groups: 70 (87.5%) patients from the case group received combined therapy versus 53 (66.2%) from the control group (p <0.01) (table 4). The first dose of antibiotic was administered within three hours of admission to the emergency room in 70% of cases but in only 27.5% of controls (p <0.01). Compliance with 2007 ATS/IDSA guidelines was obtained in 64 cases (80.0%) and in 38 controls (47.5%) (p <0.01).

The most frequent pattern of antibiotic use was a combination of a cephalosporin with a macrolide (table 5), which was administered in 65 (40.6%) patients: 38 (47.5%) in the case group and 27 (33.8%) in the control group (p 0.11).

The most frequent combination in the case group was ceftriaxone and azithromycin (26 patients, 32.5%), while in the control group it was ceftriaxone and clarithromycin (20 patients, 25.0%). The second most frequently administered antibiotic pattern was an association of a cephalosporin and a quinolone, being cefotaxime/ceftriaxone plus levofloxacin the most used combination (case group: 24 patients, 30.0%; control group: 9 patients, 11.3%).

Table 6 shows the univariate analysis for determining variables associated with ICU mortality: COPD (p 0.05), estimated probability of death (p <0.01), shock at ICU admission (p <0.01), invasive mechanical ventilation (p <0.01), acute kidney injury (0.02), rapid radiographic spread (p 0.02), combined therapy (p 0.02) and early antibiotic administration (p 0.02) differed significantly between survivors and non-survivors.

Multivariate analysis was performed to identify risk factors for mortality (table 7). Variables with significant differences from the univariate model (table 6) were introduced in this model: the need for invasive mechanical ventilation was associated with a higher risk of ICU mortality (OR 5.23, 95%CI 1.60 - 17.17); in contrast, first dose of antibiotic within three hours (OR 0.36, 95%CI 0.15 - 0.87) and combined therapy (OR 0.19, 95%CI 0.07 - 0.51) were associated with a lower risk of ICU mortality in pneumococcal SCAP. The model remained similar when the variable “Macrolide Use” was added as dependent variable in the multivariate analysis (Macrolide Use OR for death: 1.52, 95%CI 0.56-4.16).

DISCUSSION

The main finding of this study was a 15% decrease in ICU mortality due to SCAP caused by *Streptococcus pneumoniae* during the study period. Several changes in antibiotic prescription practices were detected and an association between improved survival and both earlier antibiotic administration and increased combined antibiotic therapy were identified.

The WHO's Annual Reports stress the minimal decrease in worldwide mortality secondary to lower respiratory infection: from 4.1 million (1993) to 3.9 million (2002) (27,28). Mortality due to all-source infectious diseases has increased in recent decades (29), up to a 58% in USA (30). However, its translation to clinical practice is difficult because no differentiation has been made between mild/severe infection or local/sepsis/septic shock, considering that complicated infection with systemic inflammatory response syndrome bears higher mortality than local infection (31).

In accordance with our results, there's evidence supporting that severe sepsis/septic shock mortality decreased in the last years (32): overall mortality of any-source severe sepsis had decreased in the last decade up to 12% (19,20). Explanations for this trend include higher compliance with international guidelines (33,34), better hemodynamic management (35), improved ventilator setting in mechanical ventilation (36,37), decreased ICU admissions of patients with extremely poor prognosis (19), and changes in medical treatment (35,38,39,40).

Studies showing that early antibiotic administration seems to be unrelated with better outcomes excluded critically ill patients (41,42). It has consistently been demonstrated that early antibiotic administration is a determinant of the outcome in severe sepsis and shock, regardless the source of infection (38,39,40), supporting 2012 Surviving Sepsis Campaign's recommendation on initiation of antibiotic within the first hour of the diagnosis of severe sepsis (35).

Our results show that combined antibiotic therapy is associated with lower ICU mortality, which is supported by other studies (43,44,45,46); however, most of these enrolled patients with pneumonia and shock. Our data shows improved survival in patients receiving combined therapy, both general population and in patients with shock or under mechanical ventilation (figure 3), suggesting that the benefit of combined therapy is not limited to patients with shock.

Still, it is unclear why combined therapy is superior to monotherapy; possible reasons include coverage of atypical pathogens, greater probability of covering multi-resistant microorganisms, synergies and anti-inflammatory/immunomodulatory effects of some antimicrobials. In the present study, as all cases were caused by *Streptococcus pneumoniae*, it is reasonable to assume that factors others than covering atypical pathogens or covering multi-resistant microorganisms were related to decreased mortality.

Interestingly, epidemiology of invasive pneumococcal disease changed significantly in Spain after the introduction of PCV7, where a shift in pneumococcal serotypes have been documented (serotypes not covered by the vaccine). This has been associated with more empyema and different rates of shock or respiratory failure (47,48,49). Substantial reduction in hospitalization for pneumonia among adults has been reported after introduction of the 7-valent pneumococcal conjugate vaccine (50).

As a conclusion, a significant decrease in mortality was observed in the whole population as well as in the subgroups of patients with shock and under mechanical ventilation (figure 2), even when stratified according to combined antibiotic therapy versus monotherapy (figure3), and early antibiotic treatment versus non-early antibiotic administration (figure 4). This observation is not only of academic interest: in view of these results all patients with pneumococcal SCAP requiring ICU admission should receive early treatment and combined antibiotic therapy.

Significant differences in antibiotic regimens administered to the study groups is seen (table 5), the most important being that azithromycin was not administered to the control group, because it was not available in intravenous formulation in Spain at the time of the CAPUCI I study. Also, broader spectrum antibiotic combinations was administered in controls than in cases; in the case group nearly 80% of patients received a combination of cephalosporin plus a macrolide or fluoroquinolone, whereas barely in 50% of controls, suggesting a higher compliance to guidelines in the case group. No differences in mortality were found between different antibiotic regimens.

Interestingly, our study population comes from a large prospective multicenter database and is homogeneous since all the patients were admitted to the ICU; to our knowledge, this is the first study to compare the clinical characteristics of the subset of critically ill patients with ICU pneumococcal CAP. Moreover, whereas most prior

studies evaluating antibiotic treatment in SCAP have been limited to subgroups with shock, our results showed a lower mortality rate in different populations, stressing the clinical implications of our findings.

The major limitation of the present study is its design, where prescription of antibiotics and hemodynamic resuscitation were not standardized; on the other hand, there were no significant differences between the two cohorts (Tables 1, 2).

Another important limitation is that recently several improvements have been introduced in the management of critical patients, including management of septic shock and mechanical ventilation. Even though major determinants of mortality for SCAP were included in our analysis, it was not possible to record all of these changes. Severity-of-illness was recorded with different scores; therefore, univariate and multivariate analysis adjusted severity for the "estimated risk of death" rather than a score. We acknowledge that the use of matching criteria for respiratory failure other than mechanical ventilation, such as PaO2/FiO2, may be associated with different outcomes, but this may also be influenced by other supporting measures like PEEP level or other ventilator settings. Bacteremia alone is not a good tool to predict outcome in pneumococcal pneumonia (51), for this reason this variable was not used to match cohorts. Although recent reports (47,48,49) correlated variation in serotypes with outcomes and complications, data regarding vaccination or serotypes were not recorded in our study. Finally, a selection bias may limit the generalization of findings.

CONCLUSIONS

In summary, incidence, mortality and management of severe pneumococcal pneumonia had significantly changed in the last decade: improved ICU survival was associated with earlier antibiotic prescription and increased use of combined antibiotic therapy.

REFERENCES

1) Mandell LA, Wunderink RG, Anzueto A et al. Infectious Diseases Society of America/American Thoracic Society consensus guidelines on the management of community-acquired pneumonia in adults. Clin Infect Dis. 2007; 44(2S): 27-72.

2) Welte T, Torres A, Nathwani D. Clinical and economic burden of community-acquired pneumonia among adults in Europe. Thorax. 2012; 67: 71-79.

3) Kang CI, Song JH, Kim SH et al. Risk factors and pathogenic significance of bacteremic pneumonia in adult patients with community-acquired pneumococcal pneumonia. J Infect. 2013; 66: 34-40.

4) Angus DC, Marrie TJ, Obrosky DS et al. Severe community-acquired pneumonia: Use of intensive care services and evaluation of American and British thoracic society diagnosis criteria. Am J Respir Crit Care Med. 2002; 166: 717-723.

5) Kaplan V, Angus DC, Griffin MF et al. Hospitalized community-acquired pneumonia in the elderly: age and sex-related patterns of care and outcome in the United States. Am J Respir Crit Care Med. 2002; 165: 766-772.

6) Menéndez R, Sahuquillo-Arce JM, Reyes S et Al. Cytokine activation patterns and biomarkers are influenced by microorganisms in community-acquired pneumonia. Chest. 2012; 141: 1537-1545.

7) Crisafulli E, Menéndez R, Huerta A et Al. Systemic inflammatory pattern of patients with community-acquired pneumonia with and without COPD. Chest. 2013; 143: 1009-1017.

8) Mortensen EM, Restrepo MI, Anzueto A et al. The impact of prior outpatients ACE inhibitor use on 30-day mortality for patients hospitalized with community-acquired pneumonia. BMC Pulmonary Medicine. 2005; 5: 12-18.

9) Van der Eerden MM, Vlaspolder F, de Graaff CS et al. Comparison between pathogen directed antibiotic treatment and empirical broad spectrum antibiotic treatment in patients with community acquired pneumonia: a prospective randomized study. Thorax. 2005; 60: 672-678.

10) Shefet D, Robenshtok E, Paul M et al. Empirical atypical coverage for inpatients with community-acquired pneumonia: systematic review of randomized controlled trials. Arch Intern Med. 2005; 165: 1992-2000.

11) Bodi M, Rodriguez A, Solé-Violán J et al. Antibiotic prescription for community-acquired pneumonia in the intensive care unit: impact of adherence to Infectious Disease Society of America guidelines on survival. Clin Infect Dis. 2005; 41: 1709-1716.

12) Mandell LA, Barlett JG, Dowell SF et al. Update of practice guidelines for the management of community-acquired pneumonia in immunocompetent adults. Clin Infect Dis. 2003; 37: 1405-1433.

13) Fine MJ, Smith MA, Carson CA et al. Prognosis and outcome of patients with community-acquired pneumonia: A meta-analysis. JAMA. 1996; 275: 134-141.

14) Jokinen C, Heiskanen L, Juvonen H et al. Microbial etiology of community-acquired pneumonia in the adult population of 4 municipalities in eastern Finland. Clin Infect Dis. 2001; 32: 1141-1154.

15) Jokinen C, Heiskanen L, Juvonen H et al. Incidence of community-acquired pneumonia in the population of four municipalities in eastern Finland. Am J Epidemiol. 1993; 137: 977-988.

16) Froes F. Community-acquired pneumonia in adults in mainland Portugal: incidence and mortality in hospital inpatients between 1998 and 2000. Rev Port Pneumol. 2003; 9: 187-194.

17) Trotter CL, Stuart JM, George R, et al. Increasing hospital admissions for pneumonia, England. Emerg Infect Dis. 2008; 14: 727-733.

18) Gaieski DF, Edwards JM, Kallan MJ et al. Benchmarking the Incidence and Mortality of Severe Sepsis in the United States. Crit Care Med. 2013; 41: 1167-1174.

19) Lagu T, Rothberg MB, Steingrub JS et al. Hospitalizations, costs, and outcomes of severe sepsis in the United States 2003 to 2007. Crit Care Med. 2012; 40: 754-761.

20) Kumar G, Kumar N, Taneja A et al. Nationwide Trends of Severe Sepsis in the 21st Century (2000-2007). Chest. 2011; 140: 1223-1231.

21) Rello J, Quintana E, Ausina V et al. A three-year study of severe community-acquired pneumonia with emphasis on outcome. Chest; 1993; 103: 232-235.

22) Lim W, Van der Eerden MM, Laing R et al. Defining community acquired pneumonia severity on presentation to hospital: an international derivation and validation study. Thorax. 2003; 58: 377-382.

23) Yoshimoto A, Nakamura H, Fujimura M et al. Severe community-acquired pneumonia in an intensive care unit: risk factors for mortality. Intern Med. 2005; 44: 710-716.

24) Sirvent JM, Carmen de la Torre M, Lorencio C et al. Predictive factors of mortality in severe community-acquired pneumonia: a model with data on the first 24h of ICU admission. Med Intensiva. 2013; 37: 308-315.

25) Loke YK, Kwok CS, Wong JM et al. Chronic obstructive pulmonary disease and mortality from pneumonia: meta-analysis. Int J Clin Pract. 2013; 67: 477-487.

26) Ishiguro T, Takayanagi N, Yamaguchi S et al. Etiology and factors contributing to the severity and mortality of community-acquired pneumonia. Intern Med. 2013; 52: 317-324.

27) World Health Organization. The World Health Report 2004 - Changing History. (Annex Table 2). ISBN 92 4 15265 X.

28) World Health Organization. The World Health Report 1995 - bridging the gaps. World Health Forum. 1995; 16: 377-385.

29) Hughes JM. Emerging infectious diseases: a CDC Perspective. Emerg Infect Dis 2001; 7: 494-496.

30) Yates RR. New intervention strategies for reducing antibiotic resistance. Chest. 1999; 115(3S): 24-27.

31) Levy MM, Fink MP, Marshall JC et al. SCCM/ESICM/ACCP/ATS/SIS 2001 International Sepsis Definitions Conference. Crit Care Med. 2003; 31: 1250-1256.

32) Valles J, Palomar M, Alvarez-Lerma F et Al. Evolution over a 15-year period of clinical characteristics and outcomes of critically ill patients with community-acquired bacteremia. Crit Care Med. 2013; 41: 76-83.

33) Ferrer M, Menendez R, Amaro R et Al. The impact of guidelines on the outcomes of community-acquired and ventilator-associated pneumonia. Clin Chest Med. 2011; 32: 491-505.

34) Menéndez R, Torres A, Reyes S et Al. Initial management of pneumonia and sepsis: factors associated with improved outcome. Eur Respir J. 2012; 39: 156-162.

35) Dellinger RP, Levy MM, Rhodes A et Al. Surviving Sepsis Campaign: international guidelines for management of severe sepsis and septic shock. 2012. Int Care Med. 2013; 39: 165-228.

36) The Acute Respiratory Distress Syndrome Network. Ventilation with Lower Tidal Volumes as Compared with Traditional Tidal Volumes for Acute Lung Injury and the Acute Respiratory Distress Syndrome. N Engl J Med. 2000; 342: 1301-1308.

37) Esquinas Rodriguez AM, Papadakos PJ, Carron M et al. Clinical review: Helmet and non-invasive mechanical ventilation in critically ill patients. Crit Care. 2013; 17: 223. [Epub ahead of print].

38) Gaieski DF, Mikkelsen ME, Band RA et al. Impact of time to antibiotic on survival in patients with severe sepsis or septic shock in whom early goal-directed therapy was initiated in the emergency department. Crit Care Med. 2010; 38: 1045-1053.

39) Nobre V, Sarasin FP, Pugin J. Prompt antibiotic administration and goal-directed hemodynamic support in patients with severe sepsis and septic shock. Curr Opin Crit Care. 2007; 13: 586-591.

40) Kumar A, Roberts D, Wood KE et Al. Duration of hypotension before initiation of effective antimicrobial therapy is the critical determinant of survival in human septic shock. Crit Care Med. 2006; 34: 1589-1596.

41) Waterer GW, Kessler LA, Wunderink RG. Delayed administration of antibiotics and atypical presentation in community-acquired pneumonia. Chest. 2006; 130: 11-15.

42) Bordon J, Aliberti S, Duvvuri P et Al. Early administration of the first antimicrobials should be considered a marker of optimal care of patients with community-acquired pneumonia rather than a predictor of outcomes. Int J Infect Dis. 2013; 17: e293-298.

43) Waterer GW, Somes GW, Wunderink RG. Monotherapy may be suboptimal for severe bacteremic pneumococcal pneumonia. Arch Intern Med. 2001; 161: 1837-1842.

44) Baddour LM, Yu VL, Klugman KP et al. Combination antibiotic therapy lowers mortality among severely ill patients with Pneumococcal bacteremia. Am J Respir Crit Care Med. 2004; 170: 440-444.

45) Luján M, Gallego M, Rello J. Optimal therapy for severe pneumococcal community acquired pneumonia. Intensive Care Med. 2006; 32: 971-980.

46) Naucler P, Daremberg J, Morfeldt E et al. Contribution of host, bacterial factors and antibiotic treatment to mortality in adult patients with bacteremic pneumococcal pneumonia. Thorax. 2013; 68: 571-579.

47) Burgos J, Luján M, Larrosa MN et al. Risk factors for respiratory failure in pneumococcal pneumonia. The importance of pneumococcal serotypes. Eur Respir J. 2013 Jul 11; [Epub ahead of print].

48) Burgos J, Lujan M, Falcó V et al. The spectrum of pneumococcal empyema in adults in the early 21st century. Clin Infect Dis. 2011; 53: 254-261.

49) Luján M, Gallego M, Belmonte Y et al. Influence of pneumococcal serotype group on outcome in adults with bacteremic pneumonia. Eur Respir J. 2010; 36: 1073-1079.

50) Griffin MR, Zhu Y, Moore MR. U.S. hospitalizations for pneumonia after a decade of pneumococcal vaccination. N Engl J Med. 2013; 369: 155-163.

51) Rello J, Lisboa T, Lujan M et al. Severity of pneumococcal pneumonia associated with genomic bacterial load. Chest. 2009; 136: 832-840.

TABLES AND FIGURES

Table 1: description of matched variables.

| | Case Group (n: 80) | Control Group (n: 80) |
|---|---|---|
| Age over 65 | 27 (33.8) | 27 (33.8) |
| COPD | 25 (32.2) | 25 (32.2) |
| Immunosuppression | 6 (7.5) | 6 (7.5) |
| Shock at ICU admission | 48 (60.0) | 48 (60.0) |
| Invasive mechanical ventilation | 52 (65.0) | 52 (65.0) |

Results are shown as absolute and percentage counts: n (%); COPD: Chronic Obstructive Pulmonary Disease; ICU: Intensive Care Unit.

Table 2: other demographics data and clinical presentations.

| | Case Group (n: 80) | Control Group (n: 80) | p value |
|---|---|---|---|
| Age* | 58.0 (46.0-69.8) | 57.0 (48.0-70.8) | 0.99 |
| Age under 50 | 30 (37.5) | 23 (28.7) | 0.31 |
| Age 50/64 | 23 (28.7) | 28 (35.0) | 0.50 |
| Age 65/74 | 15 (18.8) | 15 (18.8) | 1.00 |
| Age over 75 | 12 (15.0) | 14 (17.5) | 0.42 |
| | | | |
| Gender male | 50 (62.5) | 59 (73.8) | 0.17 |
| Active smoker | 39 (48.8) | 38 (48.7) | 1.00 |
| Alcohol use | 20 (25.0) | 26 (33.3) | 0.30 |
| Overweight | 8 (10.7) | 7 (8.8) | 0.79 |
| Diabetes mellitus | 9 (16.4) | 18 (22.5) | 0.51 |
| Cardiac failure | 16 (20.0) | 16 (20.0) | 1.00 |
| Cerebral vascular disease | 6 (7.5) | 8 (14.0) | 0.26 |
| Malignancy | 3 (3.8) | 3 (3.8) | 1.00 |
| | | | |
| Estimated probability of death * | 31.0 (17.0-52.0) | 24.0 (24.0-40.0) | 0.35 |
| ICU length of stay * | 10.0 (4.0-19.0) | 10.0 (4.0-17.8) | 0.97 |
| Days of mechanical ventilation * | 7.0 (2.8-18.8) | 7.5 (3.0-17.8) | 0.99 |
| Bacteremia | 29 (36.2) | 32 (40.0) | 0.75 |
| Acute kidney injury | 44 (55.0) | 31 (39.2) | 0.06 |
| Rapid radiographic spread | 39 (48.8) | 541 (51.2) | 0.87 |
| | | | |
| ICU mortality | 14 (17.5) | 26 (32.5) | 0.04 |

If not otherwise specified results are shown as absolute and percentage counts: n (%); * median (IQR 25/75); ICU: Intensive Care Unit.

Table 3: comparison between bacteremic and non-bacteremic patients.

| | Bacteremia (n: 61) | No Bacteremia (n: 99) | p value |
|---|---|---|---|
| Age* | 55.0 (46.5-64.5) | 57.0 (46.3-70.0) | 0.18 |
| Non immunocompromised | 54 (88.5) | 94 (94.9) | 0.22 |
| Immunocompromised: HIV | 5 (8.2) | 4 (4.0) | 1.00 |
| Immunocompromised: non-HIV | 2 (3.3) | 1 (1.0) | 1.00 |
| Shock at ICU admission | 43 (70.5) | 53 (53.5) | 0.05 |
| Invasive mechanical ventilation | 42 (68.9) | 62 (62.6) | 0.50 |
| Acute kidney injury | 31 (50.8) | 44 (44.4) | 0.42 |
| Rapid radiographic spread | 33 (54.1) | 47 (47.5) | 0.52 |
| Combined therapy | 47 (77.1) | 76 (76.8) | 1.00 |
| AB initiated 0 to 3 hours | 29 (47.5) | 49 (49.5) | 0.87 |
| ICU mortality | 15 (24.6) | 25 (25.3) | 1.00 |

If not otherwise specified results are shown as absolute and percentage counts: n (%); * median (IQR 25/75); HIV: Human Immunodeficiency Virus; ICU: Intensive Care Unit; AB: Antibiotic.

Table 4: characteristics of antibiotic treatment.

| | Case Group (n: 80) | Control Group (n: 80) | p value |
|---|---|---|---|
| Previous antibiotic | 10 (12.5) | 7 (8.8) | 0.61 |
| Monotherapy | 10 (12.5) | 27 (33.8) | <0.01 |
| Combined therapy | 70 (87.5) | 53 (66.2) | <0.01 |
| AB initiated 0 to 3 hours | 56 (70.0) | 22 (27.5) | <0.01 |
| AB initiated 4 to 6 hours | 16 (20.0) | 26 (32.5) | 0.11 |
| AB initiated more than 6 hours | 8 (10.0) | 32 (40.0) | <0.01 |
| Adequate according to 2007 IDSA/ATS guidelines | 64 (80.0) | 38 (47.5) | <0.01 |

Results are shown as absolute and percentage counts: n (%); AB: Antibiotic; IDSA/ATS: Infectious Diseases Society of America/American Thoracic Society.

Table 5: most frequent patterns of antibiotic treatment.

| | All patients (n: 160) | Case Group (n: 80) | Control Group (n: 80) | p value |
|---|---|---|---|---|
| Cephalosporin and macrolide | 65 (40.6) | 38 (47.5) | 27 (33.8) | 0.11 |
| Ceftriaxone/cefotaxime and azithromycin | 26 (16.2) | 26 (32.5) | 0 (0) | <0.01 |
| Ceftriaxone/cefotaxime and clarithromycin | 30 (18.8) | 10 (12.5) | 20 (25.0) | 0.07 |
| Other cephalosporin and macrolide | 9 (5.6) | 2( 2.5) | 7 (8.8) | 0.17 |
| Cephalosporin and quinolone | 37 (23.1) | 26 (32.5) | 11 (13.8) | <0.01 |
| Cefotaxime/ceftriaxone and levofloxacin | 33 (20.6) | 24 (30.0) | 9 (11.3) | <0.01 |
| Other cephalosporin and quinolone | 4 (2.5) | 2 (2.5) | 2 (2.5) | 1.00 |
| Ceftriaxone/cefotaxime | 15 (9.4) | 4 (5.0) | 11 (13.8) | 0.10 |
| Levofloxacin | 11 (6.9) | 5 (6,2) | 6 (7.5) | 1.00 |
| Miscellaneous combined therapy | 21 (13.1) | 6 (7.5) | 15 (18.8) | 0.06 |
| Miscellaneous monotherapy | 11 (6.9) | 1 (1.3) | 10 (12.4) | <0.01 |
| Overall | 160 (100) | 80 (100) | 80 (100) | |

Results are shown as absolute and percentage counts: n (%); p value calculated between case group and control group.

Table 6: univariate analysis to assess risk factors for ICU mortality due to pneumococcal SCAP.

| | Survival (n: 120) | No survival (n: 40) | OR (95% CI) | p Value |
|---|---|---|---|---|
| Age over 65 years | 37 (30.8) | 17 (42.5) | 1.20 (0.90-1.61) | 0.18 |
| Overweight | 11 (9.4) | 4 (10.5) | 1.01 (0.90-1.15) | 0.76 |
| Alcohol use | 31 (26.3) | 15 (37.5) | 1.18 (0.91-1.54) | 0.23 |
| Active smoker | 53 (44.9) | 24 (60.0) | 1.38 (0.91-2.1) | 0.10 |
| Diabetes mellitus | 19 (19.6) | 8 (21.1) | 1.02 (0.84-1.23) | 0.82 |
| Cardiomyopathy | 23 (19.2) | 9 (22.5) | 1.04 (0.86-1.26) | 0.65 |
| COPD | 32 (26.7) | 18 (45.0) | 1.33 (1.00-4.73) | 0.05 |
| Immunosuppression | 7 (5.8) | 5 (12.5) | 1.08 (0.95-1.22) | 0.18 |
| Estimated probability of death * | 24 (14-40) | 40 (24-52) | | <0.01 |
| Shock at ICU admission | 65 (54.2) | 31 (77.5) | 2.04 (1.11-3.74) | <0.01 |
| Invasive mechanical ventilation | 69 (57.5) | 35 (87.5) | 3.4 (1.46-7.92) | <0.01 |
| Acute kidney injury | 50 (41.7) | 25 (64.1) | 1.63 (1.04-2.54) | 0.02 |
| Rapid radiographic spread | 53 (44.2) | 27 (67.5) | 1.72 (1.07-2.76) | 0.02 |
| Combined therapy | 98 (81.7) | 25 (62.5) | 0.49 (0.28-0.85) | 0.02 |
| AB initiated 0 to 3 hours | 65 (54.2) | 13 (32.5) | 0.41 (0.19-0.87) | 0.02 |

If not otherwise specified results are shown as absolute and percentage counts: n (%); * median (IQR 25/75); COPD: Chronic Obstructive Pulmonary Disease; ICU: Intensive Care Unit; AB: Antibiotic.

Table 7: multivariate analysis to assess risk factors for ICU mortality due to SCAP.

| Variable | OR (95% CI) | p value |
|---|---|---|
| Invasive mechanical ventilation | 5.23 (1.60-17.17) | <0.01 |
| Rapid radiographic spread | 2.22 (0.91-5.43) | 0.81 |
| Acute kidney injury | 2.09 (0.76-5.79) | 0.15 |
| COPD | 1.78 (0.72-4.36) | 0.21 |
| Shock at ICU admission | 1.52 (0.52-4.49) | 0.45 |
| Estimated probability of death | 1.00 (0.98-1.03) | 0.81 |
| ATB initiated within 3 hours | 0.36 (0.15-0.87) | 0.02 |
| Combined therapy | 0.19 (0.07-0.51) | <0.01 |

COPD: Chronic Obstructive Pulmonary Disease; ICU: Intensive Care Unit; ATB: Antibiotic.

FIGURE LEGENDS:

Figure 1: flow diagram of patient selection and mortality in the different subgroups.

Figure 2: ICU mortality in the whole population and in different subgroups of patients (IMV: Invasive Mechanical Ventilation).

Figure 3: Kaplan-Meier survival curve stratified for monotherapy versus combined therapy: A) the whole population; B) patients with shock; C) patients under mechanical ventilation.

Figure 4: Kaplan-Meier survival curve stratified for early versus non-early antibiotic treatment: A) the whole population; B) patients with shock; C) patients under mechanical ventilation.

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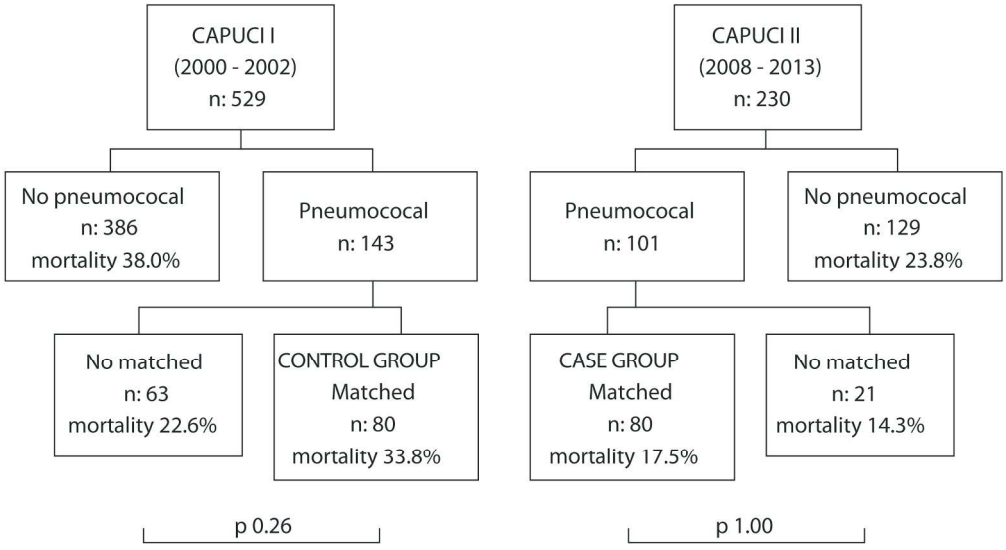


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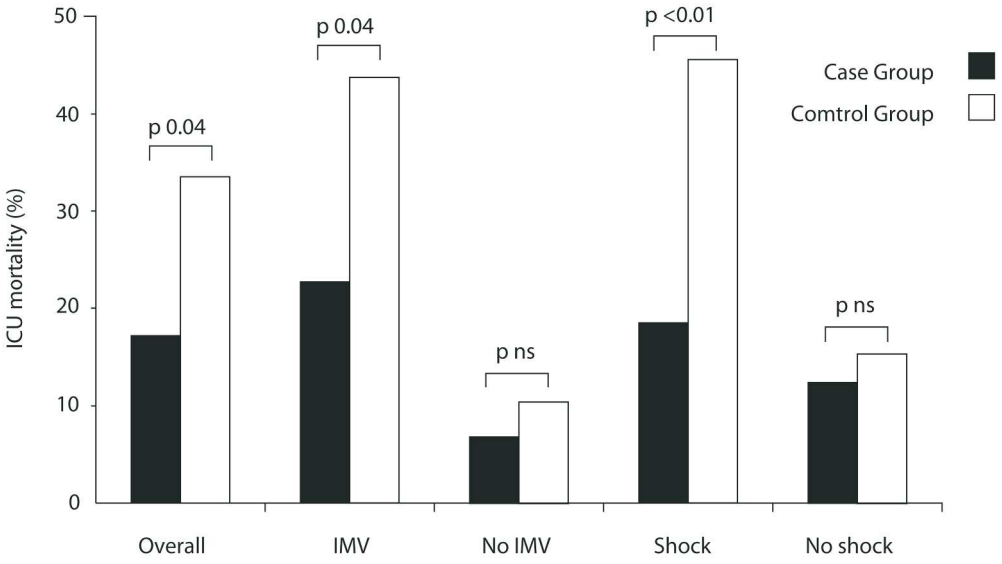


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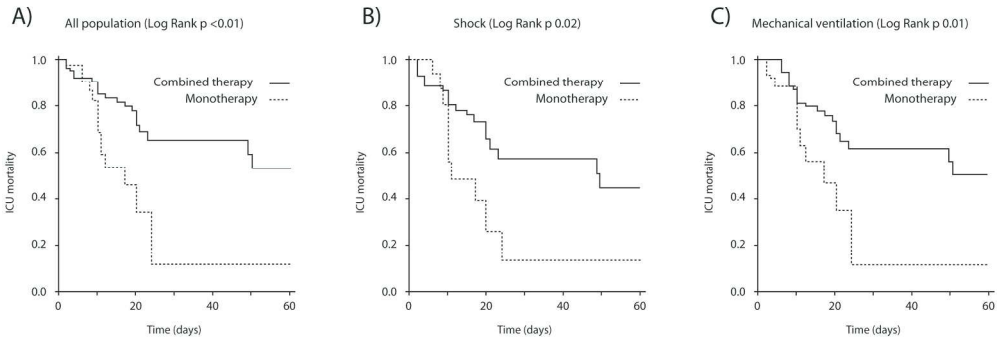


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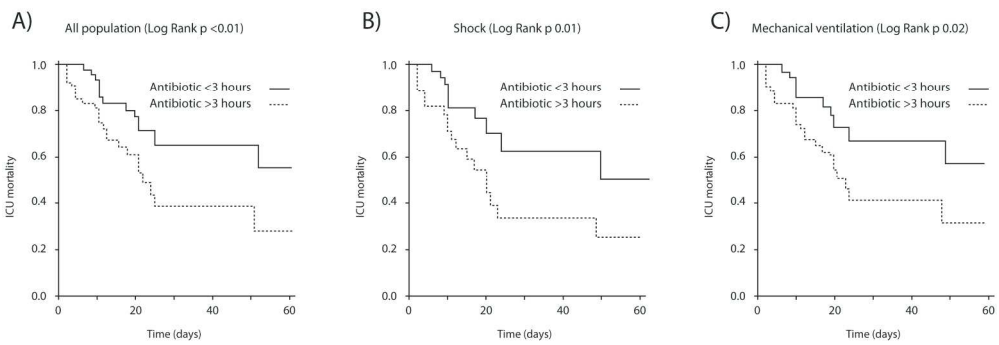


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DEFINITION:

Pneumococcal pneumonia was diagnosed when a patient had consistent clinical findings plus a new pulmonary infiltrate on chest radiography and isolation of *Streptococcus pneumoniae* in blood, pleural fluid or lower respiratory sample cultures (definite) or a positive urinary antigen test (probable). CAP was defined as an acute lower respiratory tract infection characterized by: 1) an acute pulmonary infiltrate on chest x-ray, 2) confirmatory findings of a clinical examination, and 3) acquisition of the infection outside a hospital or a long-term care facility. Severe CAP (SCAP) was defined as pneumonia that required ICU admission, with single or multi-organ failure. Probability of death was predicted according to the "estimated risk of mortality" using the APACHE II score in CAPUCI I and SAPS3 in CAPUCI II cohort, within 24 hours of ICU admission (1e,2e).

Risk factors and comorbidities were diagnosed using appropriate criteria (3e,4e,5e). Immunocompromise was defined as primary immunodeficiency or immunodeficiency secondary to radiation treatment, use of cytotoxic drugs or steroids (daily doses of >20 mg of prednisolone or equivalent for >2 weeks) (6e), transplantation or AIDS. Shock was defined as the need for a vasopressor during > 4 hours after fluid replacement; rapid radiographic spread was defined as an increase in the size of opacities on chest radiograph of >50% at 48 hours. Monotherapy was defined as administration of the same antibiotic during the first two days of ICU admission. Combination therapy was defined as administration of the same two antibiotics or more within the first two days of ICU admission. Early antibiotic administration was defined as administration of the first dose of antibiotic within three hours.

REFERENCES:

1e) Knaus WA, Draper EA, Wagner DP et al. APACHE II: a severity of disease classifica>on system. Crit Care Med. 1985; 13: 818-829.

2e) Moreno R, Philipp G, Metnitz H et al. SAPS 3: from evalua>on of the pa>ent to evalua>on of the intensive care unit. Part 2: Development of a prognos>c model for hospital mortality at ICU admission. Int Care Med. 2005; 31: 1345-1355.

3e) Rello J, Bodi M, Mariscal D et al. Microbiological tes>ng and outcome of pa>ents with severe community-acquired pneumonia. Chest; 2003; 123: 174-180.

4e) American Thoracic Society. Standards for the diagnosis and care of pa>ents with chronic obstruc>ve pulmonary disease (COPD) and asthma. Am Rev Respir Dis; 1987; 136: 225-244.

5e) Weldon BC, Monk TG. The pa>ent at risk for acute renal failure. Recogni>on, preven>on, and preopera>ve op>miza>on. Anesthesiol Clin North America. 2000; 18: 705-717.

6e) Ewig S, Ruiz M, Mensa JM et al. Severe community-acquired pneumonia: assessment of severity criteria. Am J Respir Crit Care Med; 1998; 158: 1102-1108.