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Initial Management Of Pneumonia And Sepsis. Factors associated with improved outcome.

Rosario Menéndez[1] , Antoni Torres[2] , Soledad Reyes[1], Rafael Zalacain[3], Alberto Capelastegui[4] , Javier Aspa[5] , Luis Borderías[6] , Juan J Martín-Villasclaras[7], Salvador Bello[8] , Inmaculada Alfageme[9] , Felipe Rodríguez de Castro[10] , Jordi Rello[11] , Luis Molinos[12] , Juan Ruiz-Manzano[13].

[1] Servicio de Neumología, Hospital Universitario La Fe, Valencia. CIBERES rmenend@separ.es ; reyes@comv.es
[2] Servei de Pneumologia. Institut Clinic del Torax. IDIBAPS. Universitat de Barcelona. CIBERES. GRS. ATORRES@clinic.ub.es
[3] Servicio de Neumología, Hospital de Cruces, Bilbao. rzalacain@hcru.osakidetza.net
[4] Servicio de Neumología, Hospital de Galdakao, ALBERTO.CAPELASTEGUISAIZ@osakidetza.net
[5] Servicio de Neumología, Hospital de la Princesa, Madrid jaspa@separ.es
[6] Servicio de Neumología, Hospital San Jorge, Huesca. lborderias@separ.es
[7] Servicio de Neumología, Hospital Carlos Haya, Malaga. jjvillas@gmail.com
[8] Servicio de Neumología, Hospital Miguel Servet, Zaragoza
[9] Servicio de Neumología, Hospital de Valme, Sevilla. inmaculada.alfageme.sspa@juntadeandalucia.es
[10] Servicio de Neumología. Hospital Dr. Negrín. Las Palmas de Gran Canaria frodcasw@gobiernodecanarias.org
[11] Critical Care. Hospital Vall d'Hebron. Institut de Recerca Vall d'Hebron-UAB. CIBERES jrello.hj23.ics@gencat.cat
[12] Servicio de Neumología, Hospital Central Asturias, Oviedo luismol@telefonica.net
[13] Servicio de Neumología, Hospital Germans Trias i Pujol, Badalona jruiz@separ.es

Correspondence: Rosario Menéndez, MD. Servicio de Neumología. Hospital Universitario La Fe, Avda. de Campanar 21, 46009 Valencia. Spain, Tel: (+34) 96 3862764, Fax: (+34) 96 1973089 e-mail: rmenend@separ.es

Abstract

Question. Processes of care and adherence to guidelines have been associated with improved survival in community-acquired pneumonia. In sepsis, bundles of processes of care have also increased survival. We aimed to audit in hospitalized CAP with sepsis, compliance with guideline-recommended processes of care and its impact on outcome.

Methods. We prospectively studied 4137 patients hospitalized with CAP in 13 hospitals. The processes of care evaluated were antibiotic adherence to guidelines, first dose within 6 hours and oxygen assessment. Outcome measures were mortality and length of stay.

Results. Oxygen assessment was measured in 3745 patients (90.5%), 3024 patients (73.1%) received antibiotics according to guidelines and 3053 (73.8%) received antibiotics within 6 hours. In CAP with sepsis, the strongest independent factor for survival was antibiotic adherence (odds ratio OR 0.4). In severe sepsis, only compliance to antibiotic adherence plus first dose within 6 h was associated with lower mortality (OR 0.60), adjusted for Fine prognostic scale and hospital. Antibiotic adherence was related to shorter hospital stay.

Answer to question. In sepsis, antibiotic adherence is the strongest protective factor care associated with survival and length of stay. In severe sepsis, combined antibiotic adherence and first dose within 6 hours may reduce mortality.

Word count: 200

Key words: mortality, compliance, audit, length of stay,

Introduction

The incidence of community-acquired pneumonia (CAP) ranges from 2 to 5 cases per 1000 persons [1,2] and it is the main cause of death due to infection worldwide [2]. Severe sepsis is a major healthcare problem due to its high mortality, with the main cause being CAP in hospitalized patients. In fact, up to 70 % of hospitalized CAP patients initially have sepsis or may develop sepsis during hospital stay. [3,4]

The purpose of CAP guidelines and initiatives such as the Surviving Sepsis Campaign is to provide recommendations aimed at improving patient care. Indeed, implementation of these guidelines is associated with improved quality outcomes. [5-8] The recommendations of the most recent evidence-based guidelines include several processes of care linked to improved prognosis. [9-11] In CAP, the three most recommended processes of care in the guidelines are adherence to antibiotic guidelines, first dose within 6 hours and oxygen assessment reflecting care on admission. In an audit of quality of care in hospitals in the United States, [12] blood cultures and smoking cessation advice and pneumococcal vaccination on discharge were also included. Nevertheless, in the case of blood cultures, current recommendations are aimed more at identifying a target population with a higher diagnostic yield than at a universal indication. [13]

Several prior studies have demonstrated improvements in patient outcomes based on bundles of processes of care both in CAP [5,6,14-16] and in sepsis. [17,18] However, despite the interest in analyzing the processes of care, their potential impact on prognosis is still a subject of debate. [19,20] We hypothesized that compliance with processes of care is related to better outcomes including mortality and length of stay in CAP with sepsis or severe sepsis.

The primary objective was to evaluate compliance with processes of care and the effect of each or several combinations in patients hospitalized for CAP with sepsis and severe sepsis. A second goal was to investigate its impact on survival and length of stay. We selected processes of care that depend on the care provider (physicians and nurses). Furthermore, we aimed to identify the most important combinations of processes of care that affect outcome measures.

Patients and Methods.

Design and study population

A prospective, multi-center, observational study was carried out from November 2005 to November 2007 in 13 hospitals belonging to the Spanish National Health System. Inclusion criteria were a new radiographic infiltrate compatible with the presence of acute pneumonia and at least two signs or symptoms of CAP. Exclusion criteria were admission within the previous 15 days, nursing-home patients, immunosuppressive treatment and/or steroids (>15 mg/day) and DNR orders (do not resuscitate). The study was approved by the Ethics Committees (ISS Hospital La Fe 2004/ 15 july) and the patients provided written informed consent.

We recorded data on age, gender, prior antibiotic treatment, adherence to guidelines, comorbidity and Fine risk class. [21] Follow-up was performed after discharge to assess evolution and mortality after 30 days.

Sepsis and severe sepsis were defined following previously accepted criteria [3,22] Sepsis was defined as the presence of pneumonia and systemic inflammatory response syndrome (SIRS).[3,22] Severe sepsis was considered if criteria for sepsis were met, together with acute organ dysfunction: arterial hypoxemia, creatinine > 2, acute confusion, thrombocytopenia or hyperbilirubinemia.

Processes of Care for Inpatients

The following processes of care in accordance with Spanish guidelines were recorded: 1. Assessment of arterial oxygenation on presentation (by pulse oximetry or arterial blood gas analysis); 2. Time until first antibiotic dose (< 6 hours); 3. Antibiotic adherence to the Spanish guidelines. [11] Antibiotic adherence was considered as follows: in hospitalized CAP patients, either 3rd-generation cephalosporin or amoxicillin-clavulanate combined with a macrolide or 3rd or 4th generation fluoroquinolone in monotherapy and in ICU patients, a combination of 3rd generation cephalosporin or amoxicillin-clavulanate plus macrolides or fluoroquinolone. All other regimens were considered non-adherent.

Outcome Measurements

The outcome evaluated comprised mortality during hospitalization and at 30 days. Length of stay (LOS) was defined as the number of days from admission to hospital to discharge.

Statistical Study

Univariate analysis. Statistical analyses were performed using the SAS 8.2 software program (SAS Institute, Inc, Cary, NC, USA). Categorical variables were compared using the chi-square test. Continuous variables were analyzed using the ANOVA test or the Kruskal-Wallis test. Values of $p \leq 0.05$ were considered statistically significant. In order to evaluate the effect of several processes of care in combination, we stratified patients with one process of care (adherence to SEPAR), two processes (antibiotic adherence to guidelines along with treatment within 6 hours), or three processes (antibiotic adherence, treatment within 6 hours and oxygen assessment). LOS was dichotomized as short (≤ 7 days) or long stay. PSI was categorized as low risk (I-III risk

classes) and high (IV-V). Three Kaplan-Meier survival curves were constructed to asses the effect of processes of care and sepsis status on survival.

Multivariate analysis. Several logistic regression analyses were performed for each outcome: in-hospital and 30-day mortality and LOS. For each dependent outcome variable, several logistic regression analyses were performed for the whole cohort and stratified by sepsis criteria using processes of care of one to three combinations as independent variables. We included the prognostic scale PSI and the hospital as independent variables in order to adjust for the independent effect of processes of care. The Hosmer and Lemeshow goodness-of-fit test was used to evaluate the adequacy of the models. [23] The areas under the receiver-operator characteristic (ROC) curves were also calculated.

Results

We included 4137 patients in our study after excluding 237 from nursing homes: 2966 (67.8%) had sepsis and 1572 (38%) severe sepsis. The main demographic characteristics, comorbidities and PSI scores of the population are shown in Table 1.

The overall rates for the processes of care were as follows: 3745 patients (90.5%) had oxygen assessment, 3024(73.1%) received antibiotic in accordance with the guidelines and 3053 (73.8%) received the first dose of antibiotic within 6 hours after arrival to the Emergency Department. The most frequent nonadherent regimens were: betalactams monotherapy (53% in non sepsis group, 46% in sepsis, 37% in severe sepsis) and fluorquinolone plus betalactams (27% in non sepsis group, 32% in sepsis, 36% in severe sepsis). The combination of two processes of care was observed in 53.4% of patients and three processes of care in 48.4% of patients (Table 2).

Patients with severe sepsis were more likely to receive the first dose of antibiotic within 6 hours and to have oxygen assessment whereas compliance with antibiotic

treatment recommended by the guidelines was significantly lower. Patients with severe sepsis had a higher probability of adherence to the 3 processes of care. Blood cultures were obtained in 645 (55.1%) of patients without sepsis, in 901 (64.6%) of those with non severe sepsis, and in 1044 (66.4%) of those with severe sepsis, $p<0.001$.

Outcome Measures. Univariate Results.

A total of 167 patients (4%) died during hospitalization and 214 (5.2%) died at 30 days. In-hospital mortality was 38 (2.7%) in patients with non severe sepsis and 109 (6.9%) in patients with severe sepsis, with the mortality at 30 days being 51 (3.8%) and 131 (8.5%), respectively. The results of adherence to the different isolated or combined processes of care with respect to mortality are shown in Table 3.

In-hospital mortality was significantly lower in patients with non severe sepsis who adhered to a process of care (antibiotic adherence) compared to patients who did not. An increase in the number of indicators did not reduce mortality. In patients with severe sepsis, the mortality was significantly lower (in-hospital and 30-day mortality) in those with adherence to at least 2 indicators (Table 3). LOS (expressed in medians p25-p75) was analyzed excluding patients who died in the whole group and in the groups with severe and non severe sepsis, according to adherence to the different combinations of processes of care (Table 4).

LOS was found to be one day shorter in patients with non severe sepsis and adherence to one or more processes of care. Statistically significant differences were not found in the group with severe sepsis (Tables 4-5).

In the group of patients with adherence to antibiotic treatment we analyzed the impact on mortality when the effect of other processes of care was added. The mortality tended to be lower when the first antibiotic dose was administered within the first 6 hours (p: 0.053) (Table 4). Furthermore, the Kaplan Meier survival curves comparing

survival of patients accordingly sepsis status and the effect of antibiotic adherence and timing within 6 hours are provided in Figure 1. The survival was significantly higher in patients with antibiotic compliance and timing <6h in non severe (Log Rank Mantel-Cox 9.01, p:0.01) and severe sepsis (Log Rank Mantel-Cox 9.39, p:0.009).

Multivariate Analyses

Several multivariate logistic regression analyses were carried out with the dependent variables (in-hospital mortality, mortality at 30 days and LOS). The independent variables were processes of care, entered as compliance with one (antibiotic adherence to guidelines), two or three processes of care (Table 6).

Antibiotic adherence to guidelines was the strongest protective factor for mortality in the whole population and in patients with non severe sepsis, and adding further processes of care did not improve survival. In the group with severe sepsis, the OR for the protective effect of the combination of 2 or 3 processes of care (OR 0.6. and 0.62) was better than the OR of a single process of care (OR 0.75) compared to in-hospital mortality. With regard to mortality at 30 days, only the OR for 2 processes of care maintained a trend towards lower mortality (p: 0.06). The χ^2 goodness-of-fit analysis demonstrated the adequacy of the model (p: 0.2).

In the multivariate models to predict a short stay (≤7 days) in the whole population and in the group with non severe sepsis a significant association was found with adherence to one, two or three processes of care (OR in the sepsis group 0.71, 0.71 and 0.61, respectively). No significant association was found with any process of care in the subgroup with severe sepsis.

DISCUSSION

The most important findings of our study are the following: 1. Thirty-eight percent of the patients with hospitalized CAP had severe sepsis with a 30-day mortality of 8.5% compared to <2% in those without sepsis.2. Only 48% of patients were managed with adherence to 3 processes of care and oxygen assessment was not initially performed in 10%. 3. In patients with non severe sepsis, antibiotic adherence to guidelines was the strongest independent protective factor associated with lower mortality and LOS. 4. In patients with severe sepsis the in-hospital mortality, adjusted for PSI and hospital effect, was only significantly lower when two processes of care (antibiotic adherence to guidelines and first dose within 6 hours) were followed.

In the present study we have corroborated that severe sepsis increases mortality by CAP, although our figures of mortality are lower than those reported by Dremsizov [3] (13.1% vs. 8.5%) probably due to the exclusion of nursing-home patients and are closer to those of Schaaf et al[4] in pneumococcal pneumonia. Both CAP and sepsis are the most frequent infectious causes of death worldwide and thus, the interest in developing guidelines designed to clarify their management and make recommendations regarding all the steps to be taken is not surprising. [11,18,24] Processes of care that are dependent on the actions of health care professionals play a key role, as intervention directed to implement compliance is feasible. We found that the most commonly used process was oxygen assessment and that adherence to antibiotic treatment and time until first dose were around 73%. When the results were analyzed for more than one process of care in the same patient, the percentage fell progressively in line with the increase in processes. Thus, only 48% of patients received care that adhered to 3 processes; a figure similar to that found for Mikkelsen et al in sepsis.[25] Interestingly, this percentage was higher in patients with severe sepsis (54.4%), with more patients treated within the

first 6 hours, although with lower antibiotic adherence (mainly due to a broader antibiotic spectrum).

Our findings show that antibiotic adherence to Spanish guidelines and first dose within 6 hours were associated with a lower mortality (in-hospital and at 30 days) and a lower LOS in the whole cohort. Interestingly, antibiotic adherence was the strongest protective factor for in-hospital mortality and mortality at 30 days in patients with non severe sepsis, and a further process of care did not improve outcome. On the other hand, in CAP with severe sepsis, the in-hospital mortality was only significantly reduced when both processes of care were applied.

Adherence to antibiotic treatment is the process of care that has most consistently shown a positive effect in many studies[6,7,26-28]. Moreover, in the subset of patients who received guideline-adherent antibiotic, treatment within the first 6 hours was found to significantly reduce mortality. Although it has been shown that a shorter time until antibiotic initiation improves outcome, [19] some authors have pointed out harmful consequences of this measure, such as inappropriate use of antibiotics before confirming diagnosis. [29,30] Despite the debate regarding the number of hours, we corroborated the fact that when antibiotic is administered within 6 hours, several outcome measurements are improved (in-hospital mortality in severe sepsis (p:0.05) and lower LOS in sepsis ($p<0.05$). This effect was specifically shown in patients with severe sepsis who received guideline-adherent antibiotic, which is precisely where the effect should be most evident.

Curiously, oxygen assessment has been found to be associated with higher mortality and poorer prognosis. The apparent discrepancy between this process of care and prognosis can be explained by the fact that the lack of this assessment corresponds to younger patients without comorbid conditions and, consequently, a lower mortality.

In fact, in patients with severe sepsis, oxygen assessment was complied with in nearly 98% of cases and it has been reported that early assessment in severe pneumonia improves survival. [31]

The best combination of processes of care in hospitalized patients with CAP and severe sepsis, as confirmed by the multivariate analysis, includes at least 2 processes of care (antibiotic adherence and treatment within the first 6 hours). However, in less severe patients with non severe sepsis and a single process of care (antibiotic adherence), the protective factor is very similar to that of several processes of care. This finding confirms the importance of the impact of quality and the effect of two concomitant processes of care in patients with severe sepsis. Bundles of care have been shown to increase survival in patients with sepsis of different etiologies. [17,32] Our findings, at least in the subset of patients with severe sepsis, contradict the recent recommendations of the American Academy of Emergencies that consider it useless to measure the time until the first dosage of antibiotics in CAP.[30]

LOS is an endpoint that depends on several factors related to the patient, comorbidities and social factors.[33,34] However, in the whole cohort and in patients with sepsis we consistently found that the median LOS was one day shorter if antibiotic adhered to guidelines.[35,36]

One limitation of our study is that the observational design makes it difficult to establish a cause-effect relationship between processes of care and prognosis. Their effect on outcome could be due to changes in unmeasured process of care or better medical care. [37] While it is difficult to attribute improvements in outcome to improvements in quality of care, some investigators have demonstrated improvements based on implementation of bundles of processes of care. [37] Additional measures

such as the efficiency of care during hospitalization are clearly needed, despite being difficult to describe.

In summary, we have confirmed that there are areas of improvement to increase quality care in hospitalized patients with CAP, mainly in those with severe sepsis. The message is that in CAP with severe sepsis, selection of an antibiotic and timing of the first dose within 6 hours may reduce mortality whereas in non severe sepsis, antibiotic selection is more decisive. Our findings might have clinical implications in managing hospitalized CAP in the Emergency Room. Efforts should be directed toward identifying factors that affect poorer compliance with quality indicators in order to prepare specific strategies for their resolution.

Support statement

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Table 1. Demographic Characteristics, Comorbidities and PSI Scores.

	Total	**Sepsis No.(%)**		
	N: 4137	**Non severe Sepsis**	**Severe sepsis**	**p**
		1394 (33.7)	**1572(38.0)**	
Age, mean (SD)	65.6(18.2)	61.5(19.3)	68.7(16.5)	<.001
Sex (M/F)	2740(66.2)/1397(33.8)	909(65.2)/485(34.8)	1091(69.4)/481(30.6)	.01
Smoking	926 (22.4)	349(25.0)	348(22.1)	.001
Pneumococcal vaccination	396(9.6)	106(7.6)	166(10.6)	.001
Influenza vaccination	1749(42.3)	513(36.8)	727(46.2)	<.001
Comorbidity				
Diabetes	875(21.2)	204(14.6)	305(19.4)	.001
Liver disease	176(4.3)	49(3.5)	73(4.6)	.1
Cardiopathy	591(14.3)	148(10.6)	239(15.2)	<.001
CNS disease	422(10.2)	126(9.0)	170(10.8)	.1
COPD	987(23.9)	244(17.5)	488(31.0)	<.001
PSI				
I-III/ IV-V	2240(54.1)/1897(45.9)	959(68.8)/435(31.2)	559(35.6)/1013(64.4)	<.001

Data are presented as no (%) or mean and (SD)

Definition of abbreviation: M/F: male/female, CNS: central nervous system, COPD: chronic obstructive pulmonary disease, PSI: pneumonia severity index

p. comparison between severe and non severe sepsis

Table 2. Processes of care and CAP with and without sepsis.

	Total	No sepsis	Non severe Sepsis	Severe sepsis	p
Abx	3024(73.1)	881(75.8)	1043 (75.0)	1100(70.1)	.003
Timing	3053(73.8)	814(73.6)	1012(76.8)	1227(81.3)	.004
Oxygen assessment	3745(90.5)	1050(89.7)	1164(83.5)	1531(97.4)	<.001
Abx plus timing	2208(53.4)	599(53.8)	753(56.6)	856(56.1)	.7
Abx plus timing plus oxygen assessment	2004(48.4)	539(48.0)	634(47.3)	831(54.4)	<.001

Data are presented as no (%)
Abx: Antibiotic adherence to guidelines
Timing: first antibiotic dose <6 hours
p. comparison between severe and non severe sepsis

Table 3. Mortality in CAP (in hospital and at 30 days) with or without sepsis related to compliance with processes of care.

Mortality	All	No sepsis	Non severe sepsis	Severe sepsis
Abx yes/no				
In-hospital	103(3.4)/64(5.8) [#]	15(1.7)/5(1.8)	19(1.8)/19(5.5) [#]	69(6.3)/40(8.5)
At 30 days	135(4.5)/79(7.3) [#]	23(2.6)/8(2.9)	25(2.4)/27(7.9) [#]	87(8.1)/44(9.5)
Abx plus timing yes/no				
In-hospital	68(3.1)/89(5.1)*	9(1.5)/8(1.6)	13(1.7)/23(4.0)*	46(5.4)/58(8.6) [*]
At 30 days	92(4.2)/108(6.2)*	16(2.7)/12(2.4)	18(2.4)/32(5.7)*	58(6.9)/64(9.7) [+]
Abx plus timing plus oxygen yes/no				
In-hospital	64(3.2)/93(4.7) [+]	7(1.3)/10(1.7)	12(1.9)/24(3.4)	45(5.4)/59(8.5) [+]
At 30 days	87(4.4)/113(5.8) [+]	13(2.4)/15(2.6)	17(2.7)/33(4.8) [§]	57(7.0)/65(9.5)

Data are presented as No (%)
[#]**1<= .001 * <=0.01** [+] **<0.05** [§] **: 0.051**

Abx: Antibiotic adherence to guidelines
Timing: first antibiotic dose <6 hours

Table 4. Impact of additional processes of care in patients with antibiotic adherence to Spanish guidelines.

	In-hospital Mortality No.(%)	p value	Mortality at 30 days No.(%)	p value	LOS Median (IQR)	p value
Timing <6h/>6h						
Non severe sepsis	13(1.7)/4(1.8)	.9	18(2.4)/5(2.3)	.9	6(4-9)/7(5-9)	.04
Severe sepsis	46(5.4)/18(9.0)	.053	58(6.9)/20(10.2)	.1	8(5-13)/7(5-11)	.2
Oxygen assessment yes/no						
Non severe sepsis	18(2.0)/1(0.6)	.2	24(2.8)/1(0.6)	.1	6(4-9)/7(4-10)	.08
Severe sepsis	67(6.3)/2(6.9)	.8	85(8.1)/2(7.4)	.9	8(5-12)/9(5-14)	.5
Timing plus oxygen yes/no						
Non severe sepsis	12(1.9)/5(1.4)	.6	17(2.7)/6(1.7)	.3	6(4-9)/7(4-10)	.003
Severe sepsis	45(5.4)/19(8.4)	.09	57(7.0)/21(9.5)	.2	8(5-13)/7(5-12)	.3

LOS: length of stay

Timing: first antibiotic dose <6 hours

Table 5. LOS (Expressed in medians and Interquartile range) and processes of care.

	All	No sepsis	Non severe sepsis	Severe sepsis
Abx yes/no	7(4-10)/7(5-11) [#]	6(4-9)/7(5-10) [*]	6(4-9)/7(5-11) [#]	8(5-12)/8(6-12)
Abx plus timing yes/no	7(4-10)/7(5-10) [#]	6(4-9)/7(5-10) [#]	6(4-9)/7(5-10) [#]	8(5-12)/8(5-12)
Abx plus timing plus oxygen yes/no	7(4-10)/7(5-10) [#]	6(4-9)/7(5-9) [+]	6(4-8)/7(4-10) [#]	8(5-12)/8(5-12)

Data are presented as Median(IQR)

Abx: Antibiotic adherence to guidelines

Timing: first antibiotic dose <6 hours

[#] p< 0.05 * <0.01 [+]p:0.057

Table 6. Multivariate analyses of mortality and LOS with combinations of processes of care adjusted by hospital and PSI

	In-hospital Mortality		Mortality at 30 days		LOS	
	OR (95%CI)	**p**	**OR (95%CI)**	**p**	**OR (95%CI)**	**p**
All population						
Abx	0.61(0.44-0.85)	.004	0.63(0.47-0.85)	.003	0.76(0.66-0.87)	.001
Abx plus timing	0.61(0.44-0.84)	.003	0.67(0.50-0.89)	.007	0.80(0.71-0.91)	.001
Abx plus timing plus oxygen	0.64(0.46-0.89)	.009	0.70(0.52-0.94)	.02	0.79(0.70-0.90)	.001
Non severe sepsis						
Abx	0.33(0.16-0.65)	.001	0.27(0.15-0.49)	<.001	0.76(0.59-0.97)	.03
Abx plus timing	0.47(0.23-0.95)	.03	0.44(0.24-0.82)	.009	0.73(0.58-0.92)	.007
Abx plus timing plus oxygen	0.54(0.26-1.1)	.09	0.52(0.28-0.96)	.03	0.64(0.51-0.81)	.001
Severe sepsis						
Abx	0.75(0.49-1.13)	.2	0.86(0.59-1.28)	.4	0.82(0.66-1.03)	.08
Abx plus timing	0.60(0.40-0.91)	.01	0.69(0.48-1.015)	.06	0.94(0.77-1.16)	.6
Abx plus timing plus oxygen	0.62(0.41-0.92)	.02	0.70(0.48-1.03)	.07	0.91(0.74-1.12)	.3

Abx: Antibiotic adherence to guidelines
Timing: first antibiotic dose <6 hours
OR: odds ratio CI: confidence interval

Figure 1: Kaplan –Meier survival curves in non severe sepsis (a) and severe sepsis (b) CAP patients comparing the effect of antibiotic compliance and timing <6h. CAP=community-acquired pneumonia; Abx=antibiotic.