Universidad Autónoma de Barcelona

Programa de Doctorado de Medicina Interna

TESIS DOCTORAL

IMPACTO DEL TRATAMIENTO EMPÍRICO Y ADECUACIÓN DE NORMATIVAS SEPAR EN LA NEUMONÍA ADQUIRIDA EN LA COMUNIDAD HOSPITALIZADA. ESTUDIO FARMACOECONÓMICO Y ANÁLISIS DE COSTE-EFECTIVIDAD

Tesis presentada por Soledad María Reyes Calzada para optar al grado de Doctor.
Programa de Doctorado de Medicina Interna.
Universidad Autónoma de Barcelona

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Barcelona, 09 de Noviembre 2015

AUTORIZACIÓN DEL DIRECTOR DE TESIS

La **Dra. Rosario Menéndez Villanueva**, Jefe de Servicio de Neumología del Hospital Universitari i Politècnic La Fe de Valencia.

CERTIFICA:

Que la memoria que lleva el nombre "Impacto de la adherencia a normativas SEPAR en el pronóstico de la neumonía adquirida en la comunidad. Evaluación fármaco-económica y análisis coste-efectividad", presentada por la licenciada en Medicina y Cirugía, Doña Soledad María Reyes Calzada para optar al grado de Doctor en Medicina, ha sido realizada bajo mi dirección. Una vez finalizada autorizo su presentación para ser juzgada por el tribunal correspondiente.

Y para que quede constancia a los efectos oportunos, firmo la presente en Barcelona, 09 de Noviembre 2015.

Dra. Rosario Menéndez Villanueva

AUTORIZACIÓN DEL DIRECTOR DE TESIS

El **Dr. Juan Ruiz Manzano**, Jefe de Servicio de Neumología del Hospital Germans Trials i Pujol de Badalona y Profesor Titular de la Universitat Autònoma de Barcelona.

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Y para que quede constancia a los efectos oportunos, firmo la presente en Barcelona, 09 de noviembre del 2015.

Dr. Juan Ruiz Manzano

A mis queridos padres

AGRADECIMIENTOS

Esta tesis doctoral no hubiera sido posible sin la ayuda de muchas personas, a las que quiero expresar mi más sincero agradecimiento.

En primer lugar, a los directores de esta tesis, en especial a la **Dra. Rosario Menéndez Villanueva**, por su confianza en mí desde el segundo año de médico residente en Neumología. Por su apoyo, estímulo, dedicación y cercanía. Por su ayuda tanto a nivel profesional como personal. Por sus enseñanzas en el día a día, y su constante orientación científica. Gracias porque ha sido un placer trabajar a su lado en esta ardua tarea de la investigación. Al **Dr. Juan Ruiz Manzano** por ser un privilegio que esté presente en la dirección de mi tesis doctoral. Gracias por dedicarme su tiempo, por su apoyo y colaboración.

En segundo lugar, quiero mostrar mi más sincero agradecimiento a todo el personal del **Servicio de Neumología del Hospital Universitari i Politècnic La Fe de Valencia**, médicos adjuntos, residentes, personal de enfermería, por su apoyo y facilidades dadas para la realización de este trabajo de investigación. Gracias también porque me ha permitido compaginarlo con la gratificante tarea asistencial.

A todas mis compañeras del grupo de investigación de infecciones respiratorias, **Raquel, Ángela, Alejandra, Verónica, Cristina, Luz, Paula** por aguantarme con paciencia todos estos años, por todas las horas y momentos vividos tanto los fáciles como difíciles y por la gran amistad que me une a ellas. Gracias por la sonrisa regalada de todos los días.

A mis padres, por la lucha constante. Por dedicarme gran parte de su vida y de su tiempo. Por creer en mí. Por dejarme hacer y realizar mis ilusiones. Gracias Papá y Mamá.

A Paco, Álvaro y Pablo por su apoyo incondicional, ayuda y cariño, por su compresión a pesar de los ratos robados durante estos años.

A todos ellos, muchas gracias

ÍNDICE

PRESENTACIÓN

La presente tesis está estructurada siguiendo las directrices de la normativa para la presentación de tesis doctorales como compendio de publicaciones, aprobada por la comisión de Doctorado de la Universidad Autónoma de Barcelona (UAB) en noviembre del 2004.

Los estudios que forman parte de esta Tesis Doctoral pertenecen a la misma línea de investigación. El presente trabajo está dirigido a conocer la utilidad de la implementación de las normativas de la Sociedad Española de Neumología (SEPAR) y del tratamiento empírico en la neumonía adquirida en la comunidad (NAC). Las normativas elaboradas por las sociedades científicas proporcionan una ayuda al clínico en el manejo de la infección y proporcionan una mejor calidad asistencial. Su implementación tiene efectos directos sobre la duración de la estancia, reingreso y mortalidad. De hecho, existen diferencias entre la elección de un determinado tipo de antibiótico en el pronóstico de la NAC. En nuestro trabajo se incluye una segunda parte dirigida al análisis fármaco-económico e implicación de la elección del tratamiento antibiótico empírico en términos de costes y eficacia durante la hospitalización de la NAC. Estos estudios coste-eficacia permiten evaluar la práctica clínica para maximizar el beneficio de salud frente al paciente a partir del cálculo de costes para las distintas alternativas de tratamiento.

Los resultados de los estudios incluidos han aportado información relevante y novedosa en este campo. Están recopilados en tres artículos originales que forman parte de esta tesis, publicados en revistas de amplia difusión internacional en el campo de la neumología, con un factor de impacto global de 18.358 puntos. Incluimos como material complementario el primer trabajo publicado de esta línea de investigación en el 2003 con un factor impacto de 7.636. Dichos artículos se presentan en su versión original en inglés.

Esta tesis supone una aportación desde el punto de vista clínico a la búsqueda de medidas eficaces en el tratamiento de pacientes con NAC. Este estudio ha ayudado a demostrar la eficacia de las normativas SEPAR en términos de mejora de calidad asistencial y pronóstico. Ha ayudado a demostrar la eficacia en términos de coste-efectividad de las diferentes alternativas de tratamiento según la adherencia a las directrices y como consecuencia una reducción de los costes hospitalarios.

JUSTIFICACIÓN Y OBJETIVOS DE LA TESIS

JUSTIFICACIÓN GENERAL

La neumonía adquirida en la comunidad (NAC) es una enfermedad con elevada incidencia y una de las causas más importantes de morbi-mortalidad en todo el mundo. La tasa de mortalidad bruta por neumonía se eleva a 19,05 por 100.000 habitantes en España [1] y a un 22,8 en los Estados Unidos [2]. Dichas cifras no están descendiendo en la última década,[3] por lo que se nos plantean nuevas vías de investigación para poder mejorar el pronóstico y supervivencia de la enfermedad.

La mortalidad de la NAC se relaciona con factores que dependen del paciente, de la infección, de la gravedad inicial y de factores relacionados con la actuación médica. Sin embargo, la actuación médica es un factor relacionado con el pronóstico del paciente con capacidad de ser modificado y mejorado con los beneficios que de ello se deriva.

Para ayudar al clínico en el manejo de la NAC, las sociedades científicas elaboran normativas dirigidas a mejorar el manejo del enfermo, clarificar el tratamiento empírico, e intentar eliminar la gran variabilidad en la asistencia médica entre los profesionales [4, 5]; [6] [7]. Estas normativas incluyen múltiples apartados para la atención del paciente, desde su valoración inicial hasta el alta y las medidas preventivas. La utilización de las normativas es una medida de calidad asistencial en el medio hospitalario.

En la práctica diaria, los clínicos instauramos un tratamiento antibiótico inicial adaptando las recomendaciones pautadas por las sociedades científicas a las peculiaridades epidemiológicas y del propio paciente. El impacto de la elección del tratamiento antibiótico empírico es importante por su implicación en el pronóstico. Incluso la elección de un antibiótico puede determinar la evolución de la infección [8, 9].

Por otra parte, la NAC tiene gran importancia en términos económicos. Produce gran consumo de recursos sanitarios y alto coste. Este coste puede ser directo (gasto farmacéutico, consultas médicas e ingresos hospitalarios) e indirecto (bajas laborales).[10] La duración de la estancia constituye el coste directo más importante en el coste total de la NAC hospitalizada, superior al del tratamiento antibiótico o las pruebas de laboratorio o diagnósticas. [11, 12] En los últimos años se ha constatado un interés por cuantificar, evaluar y comprobar las causas que determinan el número de días de hospitalización que

precisa una NAC. Un análisis cuidadoso de la bibliografía pone de manifiesto que la duración de la hospitalización en la NAC varía mucho entre los diferentes hospitales y depende de múltiples variables. Pero, existe escasa información dirigida a analizar específicamente la influencia de los distintos factores (elección del tratamiento, estancia hospitalaria) en los costes y menos aún conocida en términos de coste-eficacia. Estos estudios permiten evaluar la práctica clínica para maximizar el beneficio de salud frente al paciente a partir de un cálculo de costes para las distintas alternativas de tratamiento.

JUSTIFICACION Y OBJETIVOS DEL ESTUDIO 1

Reyes S, Martínez R, Cremades MJ, Martínez Moragón E, Soler JJ, Menéndez R. "Empiric treatment in hospitalized community-acquired pneumonia. Impact on mortality, length of stay and re-admission" ***(Respiratory Medicine,2007;101:1909-1915)***

Numerosos estudios publicados en la literatura destacan la importancia del seguimiento de una guía clínica en el manejo y tratamiento de la neumonía adquirida en la comunidad. El cumplimiento de una guía clínica y la elección del tratamiento empírico inicial tienen gran repercusión sobre el pronóstico y mortalidad de los pacientes hospitalizados por esta infección. Este cumplimiento repercute directamente en la calidad de la atención hospitalaria en la NAC. El efecto sobre la duración de la hospitalización, la estabilidad clínica precoz, menor mortalidad y reingresos. Incluso la utilización de determinados regímenes antibióticos utilizados en monoterapia o combinación tienen implicaciones pronósticas en la NAC.

La hipótesis de este estudio es investigar los factores que influyen en la mortalidad a los 30 días, la estancia hospitalaria y el curso de la NAC hospitalizada. En este estudio, se analiza de forma minuciosa la adherencia y seguimiento de las recomendaciones SEPAR en nuestro país. Es un estudio multicéntrico llevado a cabo en 4 hospitales de la Comunidad Valenciana. Esto nos ha permitido analizar la variabilidad de la práctica hospitalaria por los profesionales. En cuanto a los regímenes terapéuticos empleados, los hemos clasificado como adherentes y no adherentes a normativas SEPAR.

En un primer análisis univariado relacionamos la adherencia y los diferentes regímenes antibióticos administrados, con parámetros tan importantes como la mortalidad a los 30 días, duración de la estancia hospitalaria y reingreso a los 30 días. Además, hemos analizado las diferencias de estos parámetros clasificando a los pacientes según la gravedad inicial medida por escala de riesgo de Fine [13]. Esto se ha realizado entre los diferentes hospitales participantes. Posteriormente, se realizó un análisis minucioso de la mortalidad actual a los 30 días de los pacientes incluidos en el estudio, para cada pauta antibiótica. Esta mortalidad se comparó con la mortalidad a los 30 días predicha para cada clase de riesgo de Fine.

En una segunda parte del estudio se realizaron 3 estudios multivariados tipo regresión logística ajustados por gravedad inicial (Fine) para analizar que variables predecían mortalidad a los 30 días, reingreso hospitalario a los 30 días y estancia hospitalaria prolongada

-Objetivos concretos

1.- Determinar el impacto y seguimiento de las normativas españolas en la elección del tratamiento empírico en la NAC hospitalizada.

2.-Analizar el beneficio de determinados regímenes antibióticos en la evolución de la enfermedad, en cuanto a duración de estancia, mortalidad y reingreso a los 30 días.

3.-Definir que variables predicen de manera independiente tras ajustar por gravedad inicial, la mortalidad, estancia hospitalaria prolongada y reingreso hospitalario a los 30 días.

JUSTIFICACIÓN Y OBJETIVOS DEL ESTUDIO 2

Reyes S, Martínez R, Vallés JM, Cases E, Menéndez R. "Determinants of hospital costs in community-acquired pneumonia" ***(European Respiratory Journal 2008;31:1061-1067)***

La neumonía adquirida en la comunidad continúa siendo una infección de mortalidad relevante y alto consumo de recursos sanitarios. Aunque la mayoría de los episodios son tratados de forma ambulatoria, aproximadamente un 30% requieren ingreso hospitalario y es precisamente este grupo el que ocasiona aproximadamente el 90% de los costes. La gran repercusión económica se debe tanto a costes directos (medicación, pruebas de laboratorio, diagnósticas, duración de la hospitalización) como indirectos (bajas laborales). La duración de la hospitalización constituye la causa principal de los costes directos en la NAC hospitalizada.

La hipótesis del siguiente trabajo ha sido analizar los costes directos ocasionados por la NAC hospitalizada. Estos costes están influenciados por determinados factores como la edad, comorbilidad del paciente, gravedad inicial de la neumonía y complicaciones durante la hospitalización. De esta forma todos estos factores prolongan la estancia hospitalaria y consecuentemente aumentan los costes directos y totales de esta infección. Identificando estos factores que son determinantes de alto coste podríamos definir estrategias para reducción de costes o utilización más eficientes de los recursos de los que disponemos.

Es un estudio prospectivo y observacional, realizado durante 13 meses en un hospital terciario. Se han analizado de forma descriptiva todos los costes directos durante la hospitalización, clasificados en: coste de la medicación, coste de las pruebas de laboratorio, coste de las pruebas diagnósticas, coste de la duración de la estancia y coste total de la NAC. En un primer análisis univariado hemos analizado todos los costes directos según edad, comorbilidad, gravedad inicial según escala de riesgo de Fine y complicaciones. Además, hemos identificado los factores que de forma independiente predicen un alto coste en la NAC hospitalizada, definiendo alto coste como el que excedía a la mediana de la cohorte (> 1683€).

En una segunda parte del estudio, hemos realizado un análisis multivariado tipo regresión logística. Las variables independientes introducidas fueron las encontradas estadísticamente significativas en el univariado y aquellas

consideradas clínicamente relevantes. Y como variable dependiente la variable alto coste. De esta manera analizamos de forma más precisa los factores asociados a alto coste durante la hospitalización.

-Objetivos concretos

1.- Analizar desde el punto de vista de la perspectiva hospitalaria los costes directos producidos por la hospitalización de la neumonía.

2.- Evaluar la influencia de la edad avanzada, las comorbilidades, la gravedad inicial y las complicaciones en los diferentes componentes del coste.

3.-Analizar los factores que de forma independiente determinan un alto coste durante la hospitalización.

JUSTIFICACIÓN Y OBJETIVOS DEL ESTUDIO 3

Menéndez R, Reyes S, Martínez R, De la Cuadra P, Vallés JM, Vallterra J. "Economic evaluation of adherence to treatment guidelines in nonintensive care pneumonia" (*European Respiratory Journal 2007;29:751-756)*

Las guías clínicas han sido desarrolladas para mejorar el manejo de los pacientes. Numerosos estudios, analizan y encuentran resultados positivos cuando el tratamiento antibiótico se adhiere a las normativas, con mejores resultados, mejor pronóstico y menor mortalidad. [14-16] Por el contrario, existe poca información relativa al impacto de las normativas en el coste de la NAC.

En los últimos años, existe una tendencia a reducir el coste hospitalario utilizando estrategias que fomentan un alta hospitalaria precoz. Algunos autores, sugieren que esta reducción de la estancia hospitalaria puede acompañarse de un aumento de la mortalidad y reingreso a los 30 días. [17]. Estos hallazgos suponen una dificultad en la implementación de medidas directas destinadas a reducir costes sin considerar los efectos negativos en el pronóstico de los pacientes. Por ello, en la práctica clínica, la evaluación de los costes debería tener una perspectiva que incluya ambos conceptos, el coste y su efectividad. Algunos autores, analizan el impacto de las guías clínicas y los costes. Así Suchyta et al. [18] encuentran menos reingresos y costes tras la implementación de las normativas Orrick et al. [19], en pacientes hospitalizados con NAC, encuentran que el tratamiento instaurado según la normativa IDSA [6] reduce el coste, (la media del grupo tratado con antibióticos según las guías 3009 vs 4992 dólares), aunque en este estudio no se tiene en cuenta la severidad inicial, la cual es un determinante importante de la estancia hospitalaria. El análisis del coste efectividad es una herramienta útil al evaluar costes y resultados con diferentes modalidades de tratamiento. El análisis dirigido directamente al tratamiento antibiótico y adherencia a las guías clínicas apenas ha sido estudiado en la NAC.

La hipótesis del siguiente trabajo ha sido determinar si la adherencia a las directrices SEPAR para el tratamiento de pacientes con NAC hospitalizados es la alternativa más eficiente, según el análisis coste-efectividad.

El trabajo es un estudio prospectivo y observacional de 13 meses de duración en un hospital terciario. La medida de efectividad del tratamiento fue el total de pacientes curados. Los pacientes curados fueron los que no murieron ni reingresaron a los treinta días. Los costes se han calculado separadamente para los pacientes con tratamiento adherente a las guías SEPAR (grupo A) y para los

pacientes con otros regímenes terapéuticos (grupo NA). Se calcularon los cocientes de coste-efectividad para cada grupo dividiendo el coste (C) por la efectividad (E), obteniendo los siguientes cocientes C_A/E_A y C_{NA}/E_{NA}.

Posteriormente se realizó un análisis de minimización de costes: C_A-C_{NA} para calcular las diferencias en el coste por paciente entre las dos opciones. Se calculó la ratio del coste-efectividad incremental (ICER) para determinar la diferencia en costes y efectividad entre ambas alternativas (adherencia versus no-adherencia): ICER= (C_A-C_{NA}) /(E_A-E_{NA}). Esta medida es la utilizada habitualmente para comparar dos opciones de tratamiento. Por último, se realizó un análisis de sensibilidad para evaluar si los resultados eran robustos.

-Objetivos concretos

1.- Realizar una evaluación fármaco-económica para determinar la eficiencia de la adherencia a las normativas de tratamiento de la Sociedad Española de Neumología y Cirugía (SEPAR) en la neumonía adquirida en la comunidad.

2.- Determinar si el tratamiento y el manejo de pacientes hospitalizados por neumonía adquirida en la comunidad es coste-efectivo, tras cuantificar los costes desde la perspectiva hospitalaria.

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PUBLICACIONES ORIGINALES

Los resultados de los estudios que constituyen la base de la presente Tesis Doctoral han estado recopilados en las siguientes publicaciones:

- Reyes S, Martínez R, Cremades MJ, Martínez Moragón E, Soler JJ, Menéndez R. "Empiric treatment in hospitalized community-acquired pneumonia. Impact on mortality, length of stay and re-admission". *Respiratory Medicine* 2007; 101:1909-1915. (Factor de Impacto=3,086)*

- Reyes S, Martínez R, Vallés JM, Cases E, Menéndez R. "Determinants of hospital costs in community-acquired pneumonia". *Eur Respir J* 2008; 31:1061-1067. (Factor de Impacto=7,636)*

-Menéndez R, Reyes S, Martínez R, De la Cuadra P, Vallés JM, Vallterra J. "Economic evaluation of adherence guidelines in nonintensive care pneumonia". *Eur Respir J* 2007;29:751-756. (Factor de Impacto=7,636)*

Factor de Impacto global: 18,358

****Journal Citation Report Science Edition 2014***

ARTICULO 1

Respiratory Medicine (2007) **101**, 1909–1915

ELSEVIER

respiratoryMEDICINE

Empiric treatment in hospitalized community-acquired pneumonia. Impact on mortality, length of stay and re-admission ☆

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Received 17 October 2006; accepted 23 April 2007
Available online 12 July 2007

KEYWORDS
Community-acquired pneumonia;
Treatment;
Mortality;
Length of stay

Summary
Objective: To evaluate adherence to guidelines when choosing an empirical treatment and its impact upon the prognosis of community-acquired pneumonia (CAP).
Methods: A prospective multicentre study was conducted in 425 CAP patients hospitalized on ward. Initial empirical treatment was classified as adhering or not to Spanish guidelines. Adherent treatment was defined as an initial antimicrobial regimen consisting of beta-lactams plus macrolides, beta-lactam monotherapy and quinolones. Non-adherent treatments included macrolide monotherapy and other regimens. Initial severity was graded according to pneumonia severity index (PSI). The end point variables were mortality, length of stay (LOS) and re-admission at 30 days.
Results: Overall 30-day mortality was 8.2%, the mean LOS was 8 ± 5 days, and the global re-admission rate was 7.6%. Adherence to guidelines was 76.5%, and in most cases the empirical treatment consisted of beta-lactam and macrolide in combination (57.4%). Logistic regression analysis showed that other regimens were associated with higher mortality OR = 3 (1.2–7.3), after adjusting for PSI and admitting hospital. Beta-lactam monotherapy was an independent risk factor for re-admission. LOS was independently associated with admitting hospital and not with antibiotics.

☆This work has been supported by CIBER-CB06/06/0028.
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0954-6111/$ - see front matter
doi:10.1016/j.rmed.2007.04.018

Conclusions: A high adherence to CAP treatment guidelines was found, though with considerable variability in the empirical antibiotic treatment among hospitals. Non-adherent other regimens were associated with greater mortality. Beta-lactam monotherapy was associated with an increased re-admission rate.

Introduction

Community-acquired pneumonia (CAP) is one of the diseases with the greatest morbidity–mortality in the world, and leads to important consumption of health care resources. The gross mortality rate due to pneumonia is 17.2 per 100,000 inhabitants in Spain,[1] versus 20.9 in the United States.[2] These figures have not decreased in recent decades.[2,3] Mortality due to pneumonia can be related to factors depending on the infection, the causal microorganism, the initial severity of the disease, and parameters associated with medical care. The initial severity of CAP can be quantified, but is not amenable to modification. The causal microorganism is, in turn, dependent upon the geographical setting, patient co-morbidity, toxic habits, and age among others. However, medical intervention is a factor related to the patient prognosis that can be modified and improved. In this context, inadequate initial antibiotic treatment is known to be associated with important mortality.[4,5]

Prescription of antibiotics in CAP is usually an empirical selection because the causal microorganisms are unknown at diagnosis. Furthermore, neither symptoms nor analytical data or radiological findings allow an accurate etiologic diagnosis. In fact, a limitation on CAP therapy studies is that there are very few well-designed CAP treatment studies and most of them are retrospective and non-experimental.

Guidelines to aid in the decision for empirical treatment and patient management have been developed by scientific societies.[6–9] These guidelines stratify patients by age, co-morbidity, risk factors for microbial resistance and/or specific parameters for selecting the antibiotic regimen.

The choice of treatment regimen also has prognostic implications, since different therapeutic protocols exist and not all of them offer the same beneficial effects for the patient.[10–12] Thus, treatment adherence to the guidelines, and the use of certain antibiotic regimens such as macrolides plus beta-lactams and fluoroquinolones have been associated with improved outcomes.[13–17] However, the controversy remains about the beneficial impact on prognosis of empirical treatments with or without atypical coverage.[18,19] Two recently published meta-analyses have shown no beneficial effect when atypical coverage against microorganisms is prescribed.[20,21]

Our working hypothesis is that mortality, the length of hospital stay, and the course of CAP in hospitalized patients depends on hospital type and the prescription of adequate initial empirical treatment following guidelines. We therefore investigated adherence to the established Spanish guidelines when choosing an empirical antibiotic treatment, and its impact upon the prognosis of patients admitted with CAP.

Patients and methods

A prospective, observational study with a duration of one year was carried out in four public hospitals of the Autonomous Community of Valencia (Spain): a tertiary hospital (Hospital A) attending 400,000 inhabitants, and three district hospitals (B, C and D), respectively, attending 128,000, 125,000 and 54,000 inhabitants. In the tertiary hospital there is a pneumologist on duty, while in the other three hospitals there is an internist physician on duty; a radiologist on duty is found in the four centres.

The study cohort included consecutive patients admitted with CAP. The inclusion criteria were: age >18 years, symptoms of acute respiratory infection, and the presence of a new infiltrate on chest X-radiogram, with no alternative diagnosis up until resolution. Immunocompromised patients were excluded (human immunodeficiency virus infection (HIV), transplantations, and patients receiving immunosuppressing drug and/or corticosteroids at doses >20 mg/day), as were those with lung abscesses, tuberculosis, suspected aspiration, admission to hospital in the previous 15 days, and patients with pneumonia admitted to Intensive Care Unit (ICU). Informed consent was not required by our local ethics committee because no patient interventions were involved.

A protocol for data collection in the first 24 h was applied in all cases: age, sex, smoking and alcohol consumption, vaccination status, residence for the elderly, co-morbidity (pulmonary, heart, liver, neurological, renal, neoplasms and diabetes mellitus). The following clinical data were recorded: cough, expectoration, chest pain, dyspnea, mental alterations, temperature, heart rate, respiratory rate, and blood pressure. Recorded analytical data were leucocyte count, sodium, potassium, serum creatinine, glucose, GOT/GTP, and arterial blood gas analysis. Radiological parameters were also documented (radiological pattern, number of affected lung lobes, pleural effusion or cavitation). All patients were classified according to the pneumonia severity index (PSI).[22]

Empiric antibiotic treatment was that one prescribed within the first 24 h. It was classified according to adherence or not to the Spanish guidelines, Sociedad Española de Neumología y Cirugía Torácica (SEPAR)[6,7] and to the specific antimicrobial regimen used. Adherence to guidelines for patients hospitalized on ward include the following regimens: beta-lactam (cefotaxime, ceftriaxone or amoxicillin-clavulanate) plus macrolide (clarithromycin, azithromycin, erythromycin), beta-lactam (cefotaxime, ceftriaxone or amoxicillin-clavulanate) in monotherapy, and quinolones (third or fourth generation). Any other antibiotic or combination of antibiotics was considered non-adherent to guidelines. The attending physician prescribed the initial empiric antibiotic therapy. No interventions on prescribing

physicians were carried out prior or during the study about SEPAR guidelines awareness.

The length of stay (LOS) in hospital was defined as the number of days of patient admission since arrival to hospital until discharge. Follow-up was carried out 30 days after discharge to assess the course of the patient, with evaluation of the need for re-admission, and global mortality at 30 days.

Actual and predicted 30-day mortality were compared for each antibiotic treatment regimen. Actual mortality was calculated dividing the number of deaths by the number of patients given a specific antibiotic treatment. Predicted mortality for the same groups, weighted by severity, was calculated adding the predicted mortality for each patient in the group and dividing by the number of patients in that group. Predicted mortality for each patient was the one assigned to the PSI group in which the patient was classified (I = 0.1%, II = 0.6%, III = 2.8%, IV = 8.2%, V = 29.2%).[22]

Statistical analysis

A descriptive and comparative analysis was performed: univariate analysis was based on the chi-square test for qualitative variables, while the Student's *t*-test was used for quantitative variables. Non-parametric tests were used in the absence of a normal distribution. Values of $p<0.05$ were considered statistically significant.

Three multivariate stepwise logistic regression analyses were carried out. Dependent variables were mortality in the first analysis, re-admission in the second, and prolonged LOS (>8 days) in the third. The LOS was dichotomized by the median, and prolonged LOS was considered when LOS was >8 days (yes/no). Independent variables in the three analyses were PSI, admitting hospital (A, B, C, D), adherence to guidelines (yes/no) and empiric antibiotic. PSI was dichotomized as high (Fine risk classes IV and V) or low severity (classes I–III). Empiric antibiotic regimens were classified as beta-lactam monotherapy, beta-lactam plus macrolides, quinolones, macrolides monotherapy and others. Odds ratio (OR) and 95% confidence interval (CI) were calculated, and the goodness-of-fit of the models were assessed with the Hosmer–Lemeshow test.

Results

Cohort description

A total of 425 patients were included: 229 (53.9%) admitted to the tertiary centre, and 196 (46.1%) in the general hospitals. The demographic and clinical characteristics are shown in Table 1. There were no significant differences among the four hospitals in terms of co-morbidity, age and sex. However, smoking habit was more frequent in hospitals C and D, $p = 0.02$.

Antibiotic regimens

The therapeutic adherent regimens used were: beta-lactam plus macrolide ($n = 244$, 57.4%), beta-lactam monotherapy ($n = 72$, 16.9%), and quinolones ($n = 11$, 2.6%). The non-adherent treatments were classified as macrolide monotherapy ($n = 32$; 7.5%) and others ($n = 66$; 15.5%). The latter included second generation cephalosporins plus macrolides ($n = 33$, 7.7%), ciprofloxacin monotherapy ($n = 3$, 0.7%), ciprofloxacin plus macrolide ($n = 13$, 3.2%) or plus amoxicillin-clavulanate ($n = 1$, 0.2%), third or fourth generation cephalosporins plus amikacin ($n = 5$, 1.1%), imipenem ($n = 4$, 0.9%), second generation cephalosporins as monotherapy ($n = 3$, 0.7%), vancomycin plus macrolide or antipseudomonal cephalosporin ($n = 3$, 0.7%), piperacillin-tazobactam ($n = 1$, 0.2%). The distribution by groups in each hospital is reported in Table 2. The most often used treatment regimen in the four hospitals was the combination of beta-lactams and macrolides. However, this regimen was less frequent in hospital B (38.5%), where an increase was seen in the use of other regimens (31.5%), due to a higher prescription of second-generation cephalosporins plus macrolides. Treatment adherence to the SEPAR guidelines for the global patient cohort was 76.5%. Adherence differed among the hospitals, however, and was seen to be lower in hospitals B (53.4%) and C (67.2%) compared with hospitals A (83.8%) and D (84.6%), $p = 0.0001$. The distribution of the antibiotic regimens according to PSI (Table 3) was similar in the low and high-risk groups, except for macrolide monotherapy, which was more frequent among the low-risk patients (13.6% versus 3.2%).

Table 1 Demographic characteristics, co-morbidity and PSI of the study cohort.

Patients *n* (%)	425	100
Age (yr)*	69±16	
Sex (M/F)	274/151	65/35
Co-morbidity *n* (%)		
Congestive heart failure	119	28
COPD	143	34
Diabetes mellitus	85	20
Cerebrovascular disease	63	15
Kidney disease	23	5
Liver disease	23	5
Neoplasm	35	8
Smoking	77	18
Residence for the elderly	18	4
PSI *n* (%)		
I	31	7
II	52	12
III	93	22
IV	170	40
V	79	19
Adherence to SEPAR *n* (%)	325	76
LOS*	8±5	
Deaths *n* (%)	35	8
Re-admission *n* (%)	32	8

*Data are presented as mean±SD; M: male; F: female; COPD: chronic obstructive pulmonary disease; PSI: pneumonia severity index; LOS: length of stay; SEPAR: Sociedad Española de Neumología y Cirugía torácica.

Table 2 Description of empiric treatment according to age, co-morbidity, length of stay, mortality and readmission.

	Adherence to guidelines			Non-adherence to guidelines		*p*
	Beta-lactam +macrolide	Beta-lactam monotherapy	Quinolone	Macrolide monotherapy	Other regimens	
Age (yr) (mean ± SD)	70 ± 16	73 ± 14	72 ± 18	55 ± 21	70 ± 16	0.008
Co-morbidity *n* (%)						
Congestive heart failure	70 (28.7)	23 (31.9)	3 (27.3)	5 (15.6)	18 (27.3)	NS
COPD	80 (32.8)	25 (34.7)	5 (45.5)	10 (31.3)	23 (34.8)	NS
Diabetes mellitus	50 (20.6)	16 (22.2)	0	1 (3.1)	18 (27.3)	NS
Cerebrovascular disease	37 (15.2)	10 (13.9)	3 (27.3)	3 (9.7)	10 (15.4)	NS
Kidney disease	16 (6.6)	5 (6.9)	0	0	2 (3.0)	NS
Liver disease	15 (6.1)	3 (4.7)	1 (9.1)	2 (6.3)	2 (3.0)	NS
Neoplasm	18 (7.4)	8 (11.1)	2 (18.2)	0	7 (10.6)	NS
Smoking	45 (18.6)	6 (8.5)	2 (18.2)	15 (46.9)	9 (14.1)	NS
Nursing home	10 (4.1)	1 (1.4)	1 (9.1)	0	6 (9.1)	NS
LOS days (mean ± SD)	9 ± 5	11 ± 7	9 ± 5	8 ± 3	9 ± 4	NS
Mortality *n* (%)	21 (8.6)	5 (6.9)	0	0	9 (13.6)	NS
Re-admission *n* (%)	15 (6.2)	10 (13.9)	0	3 (9.4)	4 (6.1)	NS
Hospital *n* (%)[a]						
A	138 (60.3)[b]	48 (21.0)[b]	8 (3.5)	9 (3.9)[b]	26 (11.4)[b]	
B	28 (38.4)	11 (15.1)	0	11 (15.1)	23 (31.5)	
C	30 (51.7)	9 (15.5)	0	8 (13.8)	11 (19.0)	
D	48 (73.8)	4 (6.2)	3 (4.6)	4 (6.2)	6 (9.2)	
Total *n* (%)	244 (57.4)	72 (16.9)	11 (2.6)	32 (7.5)	66 (15.5)	

COPD: chronic obstructive pulmonary disease; LOS: length of stay.
[a]Comparison among hospitals of each antibiotic regimen.
[b]$p < 0.05$.

Table 3 Description and comparison of initial empirical treatment according to low or high risk class.

Antibiotic regimen	PSI I–III *n* (%)	PSI IV–V *n* (%)	*p*-Value
Beta-lactam+macrolide $n = 244$ (57%)	91 (52)	153 (61)	0.04
Beta-lactam monotherapy $n = 72$ (17%)	28 (16)	44 (18)	0.6
Quinolone $n = 11$ (3%)	4 (2)	7 (3)	0.7
Macrolide monotherapy $n = 32$ (7%)	24 (14)	8 (3)	0.0001
Other regimens $n = 66$ (16%)	29 (16)	37 (15)	0.6
Total	176 (100)	249 (100)	

PSI I–III: Pneumonia severity index (classes I–III).
PSI IV–V: Pneumonia severity index (classes IV–V).

Mortality

Overall mortality was 8.2%, with no significant differences among hospitals. Mortality in adherent group was 26 (8.2%) and in non-adherent group was 9 (8.5%) $p = 0.9$, and no differences were found after stratifying for PSI either. The global mortality for each antibiotic regimen and according to PSI is shown in Table 4. No significant differences in global mortality were seen among the different treatment regimens. In the low-risk group, higher mortality was found among the patients treated with beta-lactam monotherapy (7.1%), although it was not statistically significant. In the high-risk group (Fine classes IV–V), mortality was higher in the group administered other regimens (24.3%), $p = 0.02$. A detailed 30-day mortality analysis was made for each antibiotic regimen (Fig. 1). This figure compares actual and predicted mortality rates. Actual mortality for all antibiotic regimens was seen to be lower than the predicted value, except for the other regimens group. In this latter group, actual mortality was greater than predicted from PSI, with a 30.2% increase in deaths.

Length of stay

The median LOS was 8 days. The median LOS in adherent group and in non-adherent group was 8 days, $p = 0.6$. On analysing LOS by hospitals, shorter stays were recorded in hospital D, with a median of 6 days, $p = 0.0001$. There were no statistically significant differences in LOS with respect to the different antibiotic regimens and PSI, $p = 0.4$ (Table 4).

Table 4 Mortality, length of hospital stay and re-admission according to antibiotic treatment and PSI.

Antibiotic regimen	Mortality *n* (%)		LOS (median)[a]		Re-admission *n* (%)[b]	
	PSI: I–III	PSI: IV–V	PSI: I–III	PSI: IV–V	PSI: I–III	PSI: IV–V
Beta-lactam+ macrolide	1 (1.1)	20 (13.1)	8	8	4 (1.7)	11 (4.5)
Beta-lactam monotherapy	2 (7.1)	3 (6.8)	8	9	4 (5.6)	6 (8.3)
Quinolone	0	0	8	8	0	0
Macrolide monotherapy	0	0	8	8	1 (3.1)	2 (6.3)
Other regimens	0	9 (24.3)[c]	8	8	0	4 (6.1)
Total	3 (1.7)	32 (12.9)	8	8	9 (2.1)	23 (5.4)

PSI: Pneumonia severity index; LOS: length of stay.
[a] $p = 0.4$: comparison median LOS in low-risk patients versus high-risk group.
[b] $p = 0.07$: comparison re-admission in low-risk patients 2.1% versus 5.4% in the high-risk group.
[c] $p = 0.02$: in the high-risk group, mortality was greater in the group administered other regimens (24.3%).

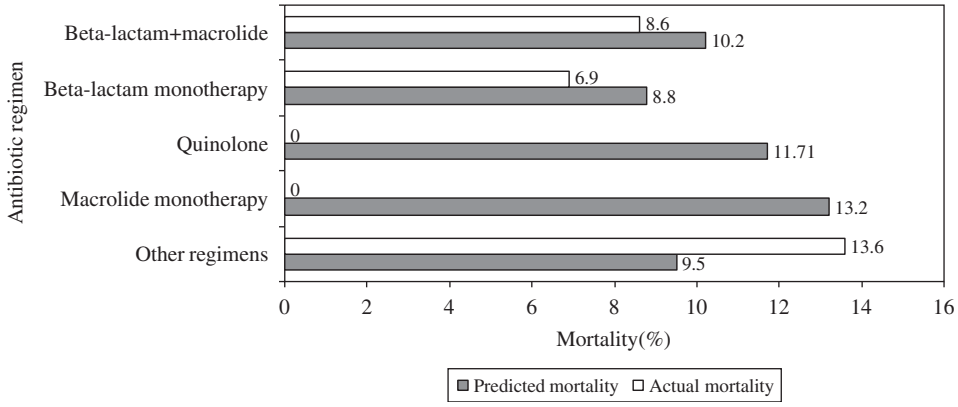

Figure 1 Actual and predicted 30-day mortality for each antibiotic regimen.

Re-admission

Thirty-two patients were readmitted within 30 days after hospital discharge (7.6%). The re-admission in adherent group was 7 (6.6%) and in non-adherent group was 25 (7.9%), $p = 0.6$. The distribution by hospitals was: 17 patients in hospital A (7.5%), 6 in hospital B (8.3%), 6 in hospital C (10.3%), and 3 patients in hospital D (4.6%), $p = 0.6$. No significant differences were found in re-admission with respect to the initial treatment regimen used. However, re-admission was related to initial severity (2.1% re-admission in low-risk patients versus 5.4% in the high-risk group), though not to a statistically significant difference ($p = 0.07$) (Table 4).

Multivariate analysis

Three logistic regression analyses were made to predict mortality, re-admission and prolonged LOS. The independent risk factors for mortality were PSI (OR = 11.1, 95% CI 2.6–48.1), and treatment with other regimens (OR = 3, 1.2–7.3). Beta-lactam monotherapy was found to be an independent risk factor for re-admission (OR = 2.7, 1.2–6.1), and in the third model, admission to hospital D was found to be protective for prolonged LOS (OR = 0.2, 0.1–0.5).

Discussion

The most relevant findings of the present study are: (1) the most widely used antibiotic regimen was the combination of beta-lactam plus macrolide, though there was considerable heterogeneity in antibiotic regimens. (2) Rates of adherence to guidelines of the SEPAR were high, but differed among the hospitals. (3) Patients treated with other regimens had an increased mortality risk (OR = 3, 1.2–7.3). (4) Beta-lactam monotherapy was independently associated with re-admission. (5) LOS was not independently influenced by empiric treatment and it was related to the admitting hospital.

The characteristics of study population were similar in all four hospitals, and similar to those of other studies of CAP in hospitalized subjects. The choice of empirical treatment was based on the guidelines of the SEPAR[6,7] in a large percentage of patients (76.5%), though with differences in adherence among the four hospitals.

The global results show the most common treatment regimen to be the combination of a beta-lactam plus macrolide, similar to the findings of other studies.[5,13] Nevertheless, it should be pointed out that in 9–31% of cases, antibiotic regimens different from those recommended by the Spanish guidelines were used. Thus, in hospital B, more alternative antibiotic regimens were prescribed, due to an increased use of second-generation cephalosporins plus

a macrolide. Although this practice does not adhere to Spanish guidelines, it does comply with the previous American guidelines.[23] Besides inertia to previous practice, Cabana et al.[24] analysed the reasons for non-adherence to guidelines. They found out many potential barriers to physician guideline adherence, including lack of awareness, familiarity, agreement, self-efficacy and outcome expectancy. In a recent publication, it has been found that other non-pneumologist specialists had a lower adherence to guidelines compared to pneumologists and residents.[25] Unfortunately, in the current study we have not specifically investigated these reasons.

The distribution of the antibiotic regimens according to PSI was similar in both the low and high-risk groups, with the exception of an increased use of macrolide monotherapy in lowest risk classes.

The mortality rate in our study (8.2%) was similar to that reported by other authors,[26–29] and was adjusted to the PSI. Noteworthy, mortality was greater (though not statistically significant) in patients administered other regimens. Other authors have previously reported lower mortality when treatment adheres to the guidelines.[4,13,30]

A detailed analysis of the antibiotic regimens employed in our study shows global mortality to be greater among the patients administered other regimens (13.6% versus 8.2%). On analysing the high-risk patients, mortality among those receiving other regimens was seen to increase significantly (24.3% versus 6.8% and 13.1%). In fact, the difference for each antibiotic regimen between actual and PSI-predicted mortality (Fig. 1) clearly reflects the increased mortality in those treated with other non-adherent regimens. The opposite was observed for the rest of antibiotic regimens, where actual mortality was lower than predicted by PSI. Likewise, other authors[4,10,14] also reported increased mortality in the group of patients administered other regimens. In the multivariate analysis to predict mortality following adjustment for PSI, other regimens were independently associated to increased mortality (OR = 3, 1.2–7.3).

In the low risk patients, mortality among those treated with macrolides and quinolones as monotherapy was lower than in those administered beta-lactam monotherapy, though statistical significance was not reached. However, these findings should be interpreted with caution, due to the few patients treated with this regimen, and in view of the low mortality inherent to low PSI.

The LOS showed no significant differences for the different antibiotic regimens. In fact, the hospital where the patient was admitted exerted greater influence. The LOS was shorter in hospital D (OR = 0.2, 0.1–0.5), and was unrelated to adherence or non-adherence to the guidelines or to the use of macrolides. Several investigators[12,15,31,32] found shorter LOS in patients treated with macrolides, though not all authors corroborate this finding.[18] Probably, the LOS is more dependent upon factors inherent to the patient and to the hospital involved.[33–35] Despite differences in LOS among hospitals, we did not find differences on mortality.[35] A clinical pathway was successful in reducing consumption of resources and LOS without causing adverse effect on mortality and re-admissions.[36]

The rate of overall re-admission was 7.6%, and tended to be greater among patients given beta-lactam monotherapy, especially in severe CAP (classes IV and V). The multivariate study showed beta-lactam monotherapy to be an independent risk factor for re-admission. Hardly any data are found in the literature on re-admission in CAP and the different antibiotic regimens used.[37]

Among the limitations of the present study, mention should be made of the few patients treated with quinolones, coincident with the withdrawal of some of these drugs (e.g., trovafloxacin) from the market. Therefore, the results of this group of antibiotics should not be extrapolated to the current situation. Since our study was not randomized, the degree of evidence is not the best, though it would not have been ethical to apply such a design in which a group of patients would be administered antibiotic regimens not recommended by the guidelines.

In conclusion, important adherence to the hospitalized CAP treatment guidelines is observed, though with considerable variability in the empirical antibiotic treatments used in daily clinical practice. Regimens not adhering to the guidelines are associated with greater mortality in CAP and not related to LOS. The beta-lactams are associated with increased re-admission, though further studies are needed to confirm this finding. LOS was related to the hospital more than to the antimicrobial treatment.

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ARTICULO 2

Eur Respir J 2008; 31: 1061–1067
DOI: 10.1183/09031936.00083107

Determinants of hospital costs in community-acquired pneumonia

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ABSTRACT: Community-acquired pneumonia (CAP) has a high incidence and involves an important consumption of healthcare resources. The present authors analysed the influence of comorbidity, initial severity and complications upon the direct costs associated with hospitalised CAP patients.

Direct hospitalisation costs (room cost, treatment, laboratory and diagnostic tests) were assessed in a prospective, observational study of 271 patients admitted to a hospital ward due to CAP.

The mean±SD patient age was 70±15 yrs. The mortality rate was 11.1%. Complications were found in 72.3% and comorbidities in 74.9%. The median (interquartile range) total cost was €1,683 (€1,291–2,471) and the component costs were: room cost €1,286 (€857–1,714); laboratory tests €212 (€171–272); treatment €187 (€114–304); and diagnostic procedures €58 (€29–122). Complications and higher Pneumonia Severity Index increased the costs, but age and comorbidity did not. A logistic regression analysis to predict high cost (>€1,683) showed that infectious (odds ratio 6.8, 95% confidence interval 1.3–36), digestive (5.9 (1.5–22.8)), pulmonary (2.6 (1.4–4.7)) and other complications (3.9 (1.8–8.4)) were independent risk factors, as were previous hospitalisation (2.3 (1.2–4.3)) and hypoalbuminaemia (2 (1.1–3.6)).

Complications, hypoalbuminaemia and previous hospitalisation were the main determinants of high direct costs of hospitalisation due to community-acquired pneumonia. Neither age nor comorbidities were independently associated with cost.

KEYWORDS: Community-acquired pneumonia, cost, length of stay, mortality, Pneumonia Severity Index, treatment

Community-acquired pneumonia (CAP) is a potentially serious disease with a high incidence and a large economic impact on both direct and indirect costs [1]. The main direct cost of the disease is due to hospitalisation of CAP patients, which can represent up to 90% of the global cost associated with CAP [2].

The global components of the direct costs of hospitalised CAP patients have been analysed recently [3, 4]. The most important components are hospital stay and antibiotic treatment, both of which are influenced by initial disease severity and the clinical course followed by the patient during hospitalisation. However, in spite of the interest in determining the causes underlying the direct costs of hospitalised CAP patients and the adoption of measures designed to restrain these costs, to date few studies have conducted a detailed analysis of the impact of comorbidities and complications. Such information is important, since patients with comorbidities and/or complications are those most often hospitalised due to CAP. Furthermore, CAP is more frequent in elderly patients with comorbidities, and worsening of comorbidities is common. In turn, this prolongs the length of hospital stay (LOS) and increases the direct costs [5, 6]. Conversely, an ageing population and increased survival among patients with chronic diseases lead to more complex CAP.

In recent years, a number of publications have analysed the economic aspects of CAP, aiming to evaluate costs in outpatients and in those admitted to the hospital or intensive care unit (ICU) [7, 8]. BAUER *et al.* [4] also found that direct costs correlated with initial severity as measured by the Pneumonia Severity Index (PSI) [9]. The present authors hypothesise that, in addition to these factors, the different components of direct costs are also influenced by comorbid conditions and complications, which would generate higher costs. Thus, identification of the determinants of high health costs could help define strategies for cost reduction or the more efficient use of existing resources [10–12].

The present study provides an analysis from the hospital perspective of the direct costs produced by the hospitalisation of CAP patients and

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Received:
August 09 2007
Accepted after revision:
December 11 2007

SUPPORT STATEMENT
This work received financial support from CIBER-CB06/06/0028.

STATEMENT OF INTEREST
None declared.

European Respiratory Journal
Print ISSN 0903-1936
Online ISSN 1399-3003

evaluates the influence of advanced age, comorbidities, PSI and complications on the different cost components. In addition, the factors causing high costs of hospitalisation due to CAP are also analysed.

PATIENTS AND METHODS

Study subjects

A prospective observational study was carried out over 13 months in a public, tertiary care university hospital (University Hospital La Fe, Valencia, Spain).

The inclusion criteria were a clinical diagnosis compatible with CAP with two or more clinical symptoms and a new infiltrate on the chest radiograph. Patients were excluded if they: were aged <18 yrs; were immunodepressed (transplant patients, HIV-infected patients with a CD4+ count of <100 cells·μL^{-1}, patients receiving immunosuppressors and/or corticoids at doses of >20 mg·day^{-1}); had lung abscesses; had been admitted to hospital in the previous 15 days; or had CAP requiring admission to the ICU.

The study was approved by the Local Ethics Committee (University Hospital La Fe). Informed consent was not necessary, since there were no interventions affecting either physicians' treatment decisions or the patients.

Definitions

Comorbidities were defined from previous studies [9, 13] as follows: cardiac (involving treatment for coronary artery disease, congestive heart failure or valvular heart disease); pulmonary (treatment for asthma, chronic obstructive pulmonary disease or interstitial lung disorders); renal (pre-existing kidney disease with documented abnormal serum creatinine levels outside the pneumonia episode); hepatic (pre-existing viral or toxic liver disease); central nervous system disorders (presence of symptomatic acute or chronic vascular or nonvascular encephalopathy, with or without dementia); diabetes mellitus (diagnosis of glucose intolerance and treatment with oral antidiabetic drugs or insulin); and neoplastic disease (any solid tumour active at the time of presentation or requiring antineoplastic treatment within the preceding year). Alcohol abuse was defined as the ingestion of an estimated amount of >80 g alcohol·day^{-1} for ⩾1 yr before presentation. Smokers were defined as current smokers of >10 cigarettes·day^{-1} for at least the preceding year.

The classification of complications was also based on previous studies [12, 14]: pulmonary (respiratory failure, arterial oxygen tension (P_{a,O_2}) <7.98 kPa (<60 mmHg), pleural effusion, pulmonary embolism, pneumothorax); cardiovascular (congestive heart failure, cardiogenic shock, acute myocardial infarction, pericarditis); digestive (gastrointestinal bleeding, diarrhoea, altered liver function); renal (acute renal failure or exacerbation of chronic renal failure); infectious (empyema: evident pus in pleural space); nosocomial infection (endocarditis, arthritis, meningitis); and other complications (diabetic decompensation, leukopaenia, anaemia, water-electrolyte disorder, cerebrovascular stroke, *etc*.).

Data collection

The following data were collected: patient age and sex, smoking and alcohol habits, influenza vaccination, nursing home residency, prior hospitalisation, and comorbidities. The clinical symptoms recorded included cough, expectoration, pleuritic chest pain, dyspnoea, acute confusion, and signs such as temperature, rales, respiratory and cardiac frequencies, and systolic and diastolic blood pressure. Laboratory parameters were also recorded: leukocyte count, sodium, potassium, serum creatinine, plasma urea, glucose, albumin, aspartate aminotransferase/alanine aminotransferase, and arterial blood gases (P_{a,O_2}, arterial carbon dioxide tension and pH). Initial severity was calculated with the PSI [9]. The following evolutive parameters were recorded: complications, LOS, and mortality after 30 days.

Cost calculations

The cost study was carried out from the hospital perspective. All the direct costs during hospitalisation were analysed, *i.e.* those related to the consumption of healthcare resources, such as diagnostic and laboratory tests, treatment and LOS. The indirect costs associated with work days missed or transport to hospital were not considered.

The tests performed during hospitalisation were quantified and classified into five groups as follows. 1) Blood tests: complete blood counts, biochemistry, haemostasis, blood gas tests. 2) Microbiological studies: blood and sputum cultures, viral serology and atypical bacteria, urinary antigens of *Legionella pneumophila* and *Streptococcus pneumoniae*. 3) Radiological studies: plain radiographs, computed tomography. 4) Endoscopic and invasive techniques: bronchoscopy, thoracocentesis, chest drainage. 5) ECGs.

The treatment provided was classified as either antibiotic treatment or other treatment. Other treatments included the treatment of comorbidities, concomitant treatment and treatment of complications. In relation to each drug used, the number of doses administered and the route of administration (oral, intravenous, intramuscular, subcutaneous or inhaled) were documented.

The LOS in hospital was calculated as the number of days of admission, from arrival at the hospital until the day of discharge.

The calculated costs were grouped as follows: 1) cost of medication, subclassified as cost of antibiotic treatment and cost of other treatments; 2) room cost; 3) cost of laboratory tests (blood tests and microbiological studies); and 4) cost of diagnostic tests (radiological studies, endoscopic and invasive techniques, and ECGs). The total hospital cost was calculated as the sum of the categories above. All costs were calculated in Euros (€) for the year 2002. The medication costs were calculated as the median cost of the drugs for the hospital during 2002 (data provided by the Pharmacy Service of the University Hospital La Fe). The costs of the radiological, microbiological and other relevant tests were obtained from the official fees of the Servicio Valenciano de Salud [15] (table 1). The cost per day of hospital stay was provided by the Servicio Valenciano de Salud for the study hospital [15].

Statistical analysis

The cost results are expressed as median (interquartile range). Qualitative variables were compared using the Chi-squared test, and quantitative variables were compared using an unpaired t-test or the Mann–Whitney U-test, where

TABLE 1 Cost of diagnostic tests

	Cost (€)
Blood tests	
Complete blood count	6.74
Biochemistry	21.40
Haemostasis	15.00
Blood gases	30.00
Microbiological tests	
Blood culture	15.52
Sputum culture, bronchial aspirate	13.39
Serology, urine antigens	5.85
Imaging techniques	
Chest or abdominal radiographs	9.23
CT	71.10
ECG	3.93
Invasive techniques	
Bronchoscopy	82.94
Thoracocentesis	54.00
Chest drainage	95.60

CT: computed tomography.

appropriate. The correlation between variables was analysed using Spearman correlation analysis. Differences in quantitative variables were assessed by ANOVA or with a Kruskal–Wallis test, as appropriate. A p-value of <0.05 was considered significant.

Uni- and multivariate statistical analyses were carried out for the clinical variables, comorbidities and complications registered in the protocol, and for high cost of CAP. High cost was defined as cost in excess of the median of the cohort (>€1,683) and was the dependent variable in a stepwise logistic regression analysis. Independent variables were those found to be significant in the univariate analysis and others considered clinically relevant, such as comorbid conditions and advanced age. Independent variables were introduced in the model and dichotomised as follows: advanced age ($\geqslant$70 yrs: yes/no); respiratory failure (P_{a,O_2} <7.98 kPa (<60 mmHg): yes/no); hypoalbuminaemia ($\leqslant$3 mg·dL^{-1}: yes/no); raised urea ($\leqslant$42 mg·dL^{-1}: yes/no), and hyperglycaemia ($\leqslant$129 mg·dL^{-1}: yes/no). PSI was categorised into high-risk classes (IV, V) or low-risk classes (I–III). The Hosmer and Lemeshow goodness-of-fit test was performed for each model [16].

RESULTS

Study population

The study included 271 patients hospitalised due to CAP, whose demographic characteristics, comorbidity, PSI [9], complications and mortality are reported in table 2. An aetiological diagnosis was reached in 35 (12.9%) patients; the most frequently found microorganisms were: *S. pneumoniae* (n=22, 8.1%), *Enterococcus faecalis* (n=3, 1.1%), *Staphylococcus aureus* (n=2, 0.7%), *Pseudomonas aeruginosa* (n=2, 0.7%), *Haemophilus parainfluenzae* (n=2, 0.7%), *L. pneumophila* (n=1, 0.4%), and other microorganisms (n=4, 1.5%). Bacteraemia was detected in 16 (5.9%) patients. Comorbidity was found in 203 (74.9%) patients, a single comorbid condition existed in 122 (45%) patients, and two or more existed in 81 (29.9%) patients. Complications, shown in table 2, appeared in 196 (72.3%) patients. Among the pulmonary complications, 100 (36.9%) patients presented with respiratory failure, and 42 (17%) presented with pleural effusion. Cardiovascular complications were congestive heart failure (n=41, 15.1%) and cardiogenic shock (n=10, 3.7%); digestive complications were liver disorders (n=7, 2.6%), bleeding (n=6, 2.2%) and diarrhoea (n=9, 3.3%); infectious complications comprised nosocomial infection (n=6, 2.2%), empyema (n=5, 1.8%), meningitis (n=1, 0.4%) and endocarditis (n=1, 0.4%). In total, 30 (11.1%) patients died.

Cost results

The median (interquartile range; IQR) total cost of the cohort was €1,683 (€1,291–2,471). The distribution of each component was as follows: room cost €1,286 (€857–1,714); laboratory tests €212 (€171–272); treatment €187 (€114–304; antibiotic treatment €138 (€81–229) and other treatments €38 (€17–68)); and diagnostic procedures €58 (€29–122). The percentage of the

TABLE 2 Demographic characteristics, comorbidity, Pneumonia Severity Index (PSI), length of stay (LOS), complications and mortality during hospital admission

Characteristics	
Subjects n	271
Age yrs	70±15
Sex M/F	161 (59.4) / 110 (40.6)
Smoker	41 (15.1)
Alcohol abuse	41 (15.1)
Nursing home	8 (3.0)
Comorbidity	
Neoplasm	13 (4.8)
Liver disease	9 (3.3)
Cardiovascular disease	89 (32.8)
Cerebrovascular disease	31 (11.4)
Kidney disease	16 (5.9)
Diabetes	57 (21.0)
COPD	69 (25.5)
PSI	
I	22 (8.1)
II	36 (13.3)
III	53 (19.6)
IV	113 (41.7)
V	47 (17.3)
LOS median days	9
Hospital complications	
Pulmonary	142 (52.4)
Renal	21 (7.7)
Cardiovascular	51 (18.8)
Digestive	22 (8.1)
Infectious	13 (4.8)
Others	55 (20.3)
Mortality	30 (11.1)

Data are presented as mean±SD or n (%), unless otherwise stated. M: male; F: female; COPD: chronic obstructive pulmonary disease.

total cost corresponding to each component was as follows: room cost 69.3%, laboratory tests 11.9%, treatment 13.1%, and diagnostic procedures 5.7%.

The median (IQR) total cost in patients with an aetiological diagnosis was significantly greater than that of patients with an unknown diagnosis (€2,102 (€1,485–3,485) *versus* €1,645 (€1,261–2,286); p=0.01). Of these, the components with significantly greater costs were: laboratory tests (€265 (€190–317) *versus* €205 (€168–262); p=0.001); diagnostic procedures (€107 (€42–234) *versus* €53 (€29–116); p=0.009); and room cost (€1,714 (€1,000–2,000) *versus* €1,143 (€857–1,714); p=0.01). No significant differences were found in the costs according to the causal microorganism. However, the median (IQR) total cost of bacteraemia patients was significantly higher compared with nonbacteraemia patients (€2,083 (€1,507–3,775) *versus* €1,628 (€1,231–2,402); p=0.04). When these were broken down into components, the costs were greater in laboratory tests (€256 (€196–384) *versus* €213 (€175–271); p=0.049) and room cost (€1,714 (€1,143–2,429) *versus* €1,143 (€857–1,714); p=0.03).

The costs according to patient age, sex, influenza vaccination, comorbidity and complications are described and compared in table 3. A tendency towards increased cost was recorded among patients >70 yrs of age, although statistical significance was not reached. The influenza vaccination was not significantly related to initial severity, LOS or costs. The median (IQR) total cost of patients without comorbidity, with a single comorbidity and with two or more comorbidities were €1,631 (€1,304–2,218), €1,637 (€1,180–2,320) and €1,771 (€1,386–2,695), respectively (p=0.03).

The direct health costs according to the PSI are reported in table 4. A positive correlation was found between the total cost (rho=0.15, p=0.009) as well as the cost of each component, except diagnostic studies, and the PSI, *i.e.* the higher the risk class, the greater the cost.

The median (IQR) total cost of uncomplicated pneumonias was €1,295 (€1,055–1,637) *versus* €1,692 (€1,392–2,083) in patients with a single complication, and €2,111 (€1,485–3,007) in patients with two or more complications (p=0.0001; table 5). The differences were significant for each of the cost components. The total costs according to the type of complication are depicted in table 3; infectious, renal and cardiovascular complications had the highest costs.

The median total cost in survivors was €1,690 (€1,294–2,313), and in nonsurvivors €1,574 (€978–3,476; p=0.9). There were significant differences in the following components of the cost between survivors and nonsurvivors: treatment (€177 (€113–281) *versus* €353 (€123–584); p=0.004); nonantibiotic treatment (€33 (€15–66) *versus* €63 (€23–271); p=0.001); and laboratory costs (€205 (€168–265) *versus* €260 (€204–298); p=0.003). However, no difference in the cost of hospital stay was found (€1,286 (€857–1,714) *versus* €1,000 (€429–2,286); p=0.1), although the LOS was greater for the survivors (median 9 days) than for the nonsurvivors (median 7 days).

Factors related to high cost

Univariate analysis

Advanced patient age, sex, toxic habits, nursing home residency and comorbidities were not significantly associated

TABLE 3 Hospital costs according to patient age and sex, and presence of comorbidities and complications

Presence of comorbidities/complications	Yes	No	p-value#
Males	1636 (1177–2392)	1812 (1370–2533)	0.2
Age ⩽70 yrs	1548 (1178–2281)	1804 (1367–2548)	0.06
Influenza vaccination	1796 (1371–2483)	1547 (1333–2786)	0.6
Comorbidities			
Neoplasm	1291 (1030–2059)	1691 (1328–2513)	0.1
Liver disease	1426 (1173–2148)	1691 (1292–2504)	0.4
Heart failure	1700 (1343–2695)	1665 (1229–2292)	0.5
Central nervous system	1833 (1291–2730)	1655 (1278–2354)	0.2
Renal disease	1696 (1337–2433)	1674 (1273–2471)	0.7
Diabetes	1700 (1378–2715)	1665 (1271–2367)	0.4
COPD	1771 (1320–2674)	1658 (1271–2274)	0.2
Complications			
Pulmonary	1996 (1394–2843)	1485 (1122–1979)	0.001
Pleural effusion	2324 (1487–3321)	1630 (1250–2206)	0.001
Respiratory failure	1846 (1380–2665)	1533 (1175–2140)	0.004
Infectious	2783 (2045–6161)	1645 (1271–2332)	0.005
Empyema	2075 (1531–2892)	1666 (1287–2427)	0.3
Nosocomial infection	3405 (1728–5716)	1659 (1282–2392)	0.06
Cardiovascular	2691 (1375–3485)	1634 (1261–2154)	0.002
Digestive	2591 (1755–3807)	1634 (1263–2275)	0.002
Renal	2744 (1414–3616)	1655 (1271–2292)	0.04
Others	2068 (1516–3607)	1620 (1182–2223)	0.0001

Data are presented as median (interquartile range) cost in Euros, unless otherwise stated. COPD: chronic obstructive pulmonary disease. #: Mann–Whitney U-test.

TABLE 4 Direct costs and Pneumonia Severity Index (PSI)

	PSI						
	Total	I	II	III	IV	V	p-value#
Medication costs	187 (114–304)	116 (64–244)	121 (64–244)	181 (129–297)	194 (123–282)	262 (136–419)	0.001
Antibiotic treatment	138 (81–229)	109 (55–173)	109 (54–216)	138 (95–237)	143 (76–213)	158 (100–290)	0.02
Other treatments	38 (17–68)	17 (4–37)	16 (7–37)	37 (21–62)	43 (20–75)	55 (23–148)	0.001
Laboratory test costs	212 (172–272)	190 (143–251)	173 (146–229)	196 (164–265)	219 (178–285)	232 (190–310)	0.001
Diagnostic test costs	58 (29–122)	65 (36–199)	60 (33–162)	52 (24–101)	65 (33–122)	73 (22–118)	0.7
Hospital stay costs	1286 (857–1714)	1071 (571–1464)	1143 (750–1429)	1143 (857–1786)	1286 (857–1786)	1429 (857–2286)	0.02
Total CAP costs	1683 (1291–2471)	1531 (1130–2053)	1602 (1078–2048)	1630 (1341–2469)	1804 (1353–2507)	1972 (1231–3297)	0.0009

Data are presented as median (interquartile range) cost in Euros, unless otherwise stated. CAP: community-acquired pneumonia. #: Spearman correlation.

with high cost in CAP. In contrast, prior hospitalisation was associated with higher cost (median €1,624 *versus* €1,888; p=0.01). A higher PSI was also associated with high cost (p=0.01; table 4). The laboratory test disorders found in patients with high costs were: raised urea (p=0.01), hyperglycaemia (p=0.007), respiratory failure (p=0.002), and hypoalbuminaemia (p=0.0001). The median cost of all complications (pulmonary, infectious, cardiovascular, digestive, renal and others) was significantly associated with high cost (p=0.0001).

Multivariate analysis

The following independent variables were included in the model because they proved significant in the univariate analysis: prior hospitalisation, respiratory failure, hypoalbuminaemia, raised urea, hyperglycaemia, PSI and complications. Advanced age and comorbidities (found to be nonsignificant) were also included because they were study objectives. The mathematical model selected the following variables as being associated with high cost (table 6): infectious, digestive, pulmonary and other complications, hypoalbuminaemia and prior hospital admission. The Chi-squared goodness-of-fit analysis demonstrated the adequacy of the model (p>0.05).

DISCUSSION

The most relevant findings of the present study can be summarised as follows. 1) The median (IQR) total cost of hospitalised CAP patients was €1,683 (€1,291–2,471), and LOS generated the highest direct cost (69.3%). 2) Complications, particularly of an infectious nature, significantly and independently increased the direct costs of hospitalised CAP patients. 3) Neither patient age nor comorbidities was independently associated with high cost. 4) Hospital admission in the preceding year and hypoalbuminaemia also raised costs.

The annual financial burden of pneumonia was estimated by the European Respiratory Society to be €10.1 billion in Europe; in-patient care costs accounted for €5.7 billion of this amount [1]. In Spain, MONGE and co-workers [17, 18] recorded 53,000 annual hospital admissions due to CAP, with an annual healthcare cost of ~€115 million. In the present study, the documented costs were slightly higher than those reported in the national and European literature. In other studies carried out in Spain, the direct costs of in-patient care were €1,210 [8] and €1,553 [7]. In Europe, the direct costs ranged from €1,333 in Germany [4] to €2,550–7,650 in the UK [19]. Nevertheless, the European costs were significantly lower than those reported for hospitals in the USA, despite longer average stays [3, 20, 21]. In a prospective study of four hospitals in the USA, FINE *et al.* [3] recorded a median total cost of €4,468 for hospitalised CAP patients.

Hospital admission due to CAP is dependent upon a number of factors, such as PSI, comorbidities and complications. In elderly subjects, admission is decided based on the associated comorbidities and complications, both of which are more frequent in this population group [21–23]. However, in young adults, an increased probability of admission is determined by the presence of serious complications and, to a lesser extent, by comorbidities [22, 24].

The contribution of each of these factors, comorbidities, PSI and complications, to the total cost of hospitalised CAP patients has not been extensively investigated, although previous studies have analysed the effect of patient age. BARTOLOMÉ *et al.* [7] reported significantly higher costs in patients >65 yrs of age, although no details were provided on the impact of severity or comorbidities. Likewise, NIEDERMAN *et al.* [23] also found in-patient cost in patients aged >65 yrs to reach US$305 million *versus* US$192 million in those <65 yrs of age. This difference in cost was fundamentally attributable to the higher percentage of admissions and the longer duration of stay for more elderly subjects. However, the impact of comorbidity on cost was only confirmed in those patients requiring respiratory services, possibly in relation to the longer LOS. While the results of the present study show a tendency towards increased cost among patients aged >70 yrs, the difference did not reach statistical significance, and age was not selected as an independent variable by the multivariate analysis. Moreover, the presence of two or more comorbidities did not cause a significant increase in hospital costs.

In the present study, an increase in total cost was shown for patients with increased severity of CAP, and for patients with more complications. BAUER *et al.* [4] reported greater costs for patients with severe pneumonia requiring admission to ICU, compared with patients with less severe pneumonia, mainly due to longer LOS in hospital (US$2,300 *versus* US$1,242; p<0.001). KAPLAN *et al.* [22] also found patients with complicated CAP

TABLE 5 Direct costs of community-acquired pneumonia (CAP) according to the presence of complications

	Complications			p-value#
	0	1	⩾2	
Medication costs				
Antibiotic treatment	115 (64–155)	139 (90–222)	155 (87–290)	0.0001
Other treatments	20 (8–39)	36 (18–56)	57 (23–130)	0.0001
Laboratory test costs	174 (153–212)	219 (178–277)	239 (189–310)	0.0001
Diagnostic test costs	42 (22–69)	53 (19–84)	97 (33–218)	0.0001
Hospital stay costs	1000 (714–1286)	1286 (1000–1571)	1429 (1000–2286)	0.0001
Total CAP costs	1295 (1055–1637)	1692 (1392–2083)	2111 (1485–3007)	0.0001

Data are presented as median (interquartile range) cost in Euros, unless otherwise stated. #: Kruskal–Wallis test.

(admission to ICU or the need for mechanical ventilation) to require longer hospital stays, resulting in increased costs compared with patients with uncomplicated CAP (US$8,725 *versus* US$3,754). Although the present study did not include patients admitted to the ICU, an increased cost in patients with a high PSI, due to an increased number of tests and a longer LOS, was confirmed. KAPLAN *et al.* [22] also found that patients >65 yrs of age with comorbidity presented more complications. However, this finding is also explained by the fact that the PSI was higher in this group.

The percentage of complicated pneumonias in the present cohort of patients was high (72.3%), similar to the figures reported in the literature [14]. Infectious complications caused the highest direct total costs, particularly nosocomial infection (€3,405). It is well known that, while the incidence of nosocomial infection is low in CAP, it is a cause of treatment failure and seriously worsens the prognosis [13]. The present authors found this complication to increase the cost up to six-fold, due to the need for more tests and treatments, and, especially, due to a prolongation of LOS [25]. However, the absolute impact of pulmonary, cardiac and renal complications on the global cost of CAP was higher, since they produced significant cost increases, and mainly because their incidence was much higher. Furthermore, it was not uncommon to find more than one complication, a condition which in turn generated a greater cost increase.

TABLE 6 Independent factors associated with high cost#

	OR (95%CI)
Previous hospital admission	2.3 (1.2–4.3)
Hypoalbuminaemia	2.0 (1.1–3.6)
Infectious complications	6.8 (1.3–36)
Digestive complications	5.9 (1.5–22.8)
Pulmonary complications	2.6 (1.4–4.7)
Other complications	3.9 (1.8–8.4)

OR: odds ratio; CI: confidence interval. #: more than median total cost (€1,683) of community-acquired pneumonia.

The multivariate analysis confirmed that infectious (odds ratio (OR) 6.8), digestive (OR 5.9), pulmonary (OR 2.6) and other complications (OR 3.9) are the strongest independent risk factors for high cost. In addition, two other variables with independent effects were identified in the mathematical model: hypoalbuminaemia (OR 2.0) and previous hospital admission (OR 2.3). Low plasma albumin is associated with more severe CAP, and is common in the elderly. It contributes to a slower clinical response to treatment and a poorer prognosis [6, 26]. CABRÉ *et al.* [27] found prior hospitalisation to be a predictor of poor patient course and increased mortality after 30 days. One of the possible explanations for this is that prior hospitalisation is more frequent in older patients [28]. The advanced age predisposes them to more serious conditions, the appearance of more complications and greater mortality [27, 29, 30]. However, the existing literature does not show a direct relationship between prior hospitalisation and hospital costs, although all of these factors produce an increase in the total cost of the CAP. Curiously, neither age nor comorbidity was independently associated with increased in-patient cost. Similar observations apply to PSI, the effect of which also disappeared in the multivariate analysis. Thus, the hospital cost of CAP was not significantly increased in patients with comorbidities, or even with a high PSI, if they had no associated complications.

In conclusion, complications, hypoalbuminaemia and previous hospital admission were the most important determinants of high cost associated with hospitalised community-acquired pneumonia patients. However, neither patient age nor comorbidities contributed to raising the direct costs. The Pneumonia Severity Index alone was not an independent risk factor for high cost either. Strategies designed to prevent complications during hospital stay, and early management of the complications that appear, may contribute to reducing in-patient costs in hospitalised cases of community-acquired pneumonia.

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ARTICULO 3

Eur Respir J 2007; 29: 751–756
DOI: 10.1183/09031936.00052506

Economic evaluation of adherence to treatment guidelines in nonintensive care pneumonia

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ABSTRACT: Guidelines have been developed to improve the treatment of community-acquired pneumonia (CAP) but information regarding their influence on costs is lacking. The aim of the present study was to conduct a cost-effectiveness analysis of CAP treatment from the hospital perspective when adhering to Spanish guidelines.

A prospective cohort study was performed in 271 patients with CAP admitted to a tertiary-care hospital, not needing intensive care. Collected data included patients' characteristics, comorbidity, initial risk class, resource use (medication, blood and microbiological analyses, and radiology) and economic data. Antimicrobial treatment was recorded as adherent or nonadherent to Spanish guidelines. Outcome measures were mortality and readmission at 30 days.

The median cost for adherent treatment was 1,665.5 *versus* 1,710.5 Euros for nonadherent treatment. Mortality and readmission were 10% and 2.1% for adherent treatment *versus* 13.6% and 6.2% for nonadherent treatment. The cost-effectiveness ratio was 2,277 Euros per expected cure for patients treated according to the guidelines and 2,567 Euros per expected cure for the nonadherence group. The incremental cost-effectiveness ratio showed that adherence to treatment guidelines saved 1,121 Euros per patient cured compared with nonadherence. The sensitivity analysis demonstrated that the findings were robust.

An antimicrobial treatment according to guidelines is the dominant alternative due to its cost-effectiveness.

KEYWORDS: Cost-effectiveness, mortality, pneumonia, readmission, treatment guidelines

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Received:
April 17 2006
Accepted after revision:
September 09 2006

STATEMENT OF INTEREST
None declared.

Community-acquired pneumonia (CAP) is a frequent and serious disease with important socioeconomic impact. The incidence in adults is 160×10^5 cases·yr^{-1} and is the main cause of death from infection in the USA and Europe [1, 2]. Healthcare resource consumption is high and involves direct and indirect health costs, the latter due mainly to lost work days.

The impact of the cost of the disease process on the healthcare budget is mainly caused by the cost of hospitalisation, which represents 70–90% of the total cost of CAP [3, 4]. In Spain, the cost of respiratory infection is ~115 million Euros·yr^{-1} [5].

Direct health costs caused by CAP were assessed by FINE *et al.* [6] and were identified as belonging to categories such as emergency treatment, laboratory analyses, diagnostic procedures, hospital stay and other incidental procedures. Hospital stay is responsible for the highest percentage and can reach 70% of the total cost. The most recent guidelines for the management of CAP present recommendations regarding hospitalisation and discharge from hospital [7].

In order to decrease costs, there has been a tendency in recent years to reduce hospital stay using strategies that encourage early discharge [8–10]. However, METERSKY *et al.* [11] found that the progressive reduction in the duration of hospital stay was accompanied by an increase in CAP-associated mortality at 30 days and in re-hospitalisation. These findings highlighted the difficulty in implementing measures directed towards restricting costs without considering its possible negative effect on disease prognosis. The evaluation of costs in clinical practice should have a perspective that includes both concepts, *i.e.* cost and effectiveness.

Scientific societies in Europe (*e.g.* European Respiratory Society) and the USA (*e.g.* American Thoracic Society) have published practice guidelines that include recommendations for empirical

European Respiratory Journal
Print ISSN 0903-1936
Online ISSN 1399-3003

antibiotic treatment. When the antibiotic treatment adheres to these guidelines better outcomes have been achieved with lower mortality rates. However, less is known regarding the impact on costs [12, 13]. There is a dearth of information in existing CAP guidelines on the cost-effectiveness of the recommended antibiotic treatments [14] and future guidelines will need to contain this information or, at least, an evaluation of the different care options.

The objective of the present study was to conduct a pharmacoeconomic evaluation to determine if treatment adherence to the Spanish Society of Pneumology and Thoracic Surgery (SEQ-SEPAR) guidelines [15] is efficacious and whether it is cost-effective in the management of patients hospitalised with CAP, quantifying the costs from the perspective of the hospital.

PATIENTS AND METHODS

Design and study population

A prospective observational study of 13 months of duration was performed in a cohort of patients admitted to a public tertiary-care hospital. The inclusion criteria were: 1) age >16 yrs; 2) clinical picture compatible with CAP, with two or more of the following signs or symptoms: fever, new or increasing cough or sputum production, dyspnoea, pleuritic chest pain, new focal signs on chest examination; and 3) appearance of a new infiltrate in a simple chest radiography [16]. The exclusion criteria were: hospitalisation in the previous 10 days, admission to the intensive care unit (ICU), immunosuppression due to medication (except corticotherapy <15 mg·day^{-1}), HIV positive infection, bronchoaspiration or tuberculosis. The study was approved by the local ethics committee. Informed consent was not considered necessary since there was no intervention on the process of treatment of CAP or on physicians' decisions.

Data collection included demographic and clinical data: age, sex, comorbidity (diabetes mellitus, chronic heart failure, chronic obstructive pulmonary disease, cerebrovascular disease, renal disease, liver disease or neoplasia), findings in the physical examination on admission (cardiac frequency, respiratory rates, temperature, blood pressure, mental status), laboratory tests (arterial blood gases, haematocrit, leukocyte count, glycaemia, blood urea, electrolytes and others), microbiological tests, radiographic studies and other relevant procedures. All the patients were classified according to initial severity according to the risk scale of Fine [17]. Initial empirical treatment was considered to comply with the Spanish guidelines [15] when it consisted of third-generation cephalosporin (cefotaxime or ceftriaxone) or amoxycillin-clavulanic acid in combination (optional) with a macrolide, or monotherapy with fluoroquinolone (third or fourth generation). All other antibiotic regimens were considered as nonadherent to the guidelines.

Statistical analysis

A descriptive analysis of the study group was carried out and parametric statistical analyses were used if the variable had a normal distribution and nonparametric analyses if not. The Chi-squared test was used for qualitative variables. The Mann–Whitney U-test was used for quantitative variables.

Methodology for the pharmacoeconomic assessments

Costs analysis

The analyses of costs were conducted from the perspective of the hospital. Direct health costs were identified and grouped into: 1) costs of pharmacotherapy (all doses of antibiotics and any other medication for treatment of comorbidity or complications); 2) diagnostic tests (including blood gas analysis, laboratory tests, blood cultures, other microbiological studies, ECG, chest radiographs and other incidental analyses); and 3) hospital room cost (cost per day multiplied by the number of days of stay).

All the costs were calculated in Euros for the year 2002. The medications costs were calculated using the mean cost of the drugs during the year 2002. The costs of the radiographic studies and of microbiological and other relevant tests, as well as the cost per day of hospital room, were obtained from the official fees of the Valencia Health Service (Official Bulletin DOGV No. 4409 [18]), the public healthcare provider of the present authors' region.

Effectiveness: outcome measures

The measure of overall effectiveness of treatment was the total number of patients cured. A patient was considered cured when they survived the episode of pneumonia and did not require readmission for 30 days.

Cost-effectiveness and cost-minimisation analysis

Cost was calculated separately for patients with treatment complying with the SEPAR guidelines (adherence group: A) and patients treated under other regimens (nonadherence group: NA). The total individual cost for groups A and NA can be calculated as the sum of the direct costs for each patient in groups A and NA. The overall cost for groups A and NA can be calculated as the sum of the costs for all patients in groups A and NA. The quotient of cost (C) divided by effectiveness (E), *i.e.* cost-effectiveness ratios C_A/E_A and C_{NA}/E_{NA}, was calculated for both groups of patients by dividing the mean cost per patient by the probability of success for each group. The result is the mean cost per expected cure.

A cost-minimisation analysis was performed as follows: $C_A - C_{NA}$ in order to calculate the difference in costs per patient between the two options. The incremental cost-effectiveness ratio (ICER) was also calculated (Equation 1). It is defined as the ratio of the difference in costs to the difference in effectiveness between two alternatives: adherence *versus* nonadherence:

$$ICER = (C_A - C_{NA})/(E_A - E_{NA}) \quad (1)$$

The ICER is the measure primarily used to compare the cost-effectiveness of a experimental treatment with a control treatment. A bootstrap nonparametric method for calculating confidence intervals (CI) for cost-effectiveness ratios was used [19].

Sensitivity analysis

Sensitivity analysis was performed to evaluate the robustness of the results. The procedure involves modifying the data input variables using a wide range of values, usually applied to cost variables, and is a measure of the internal and external validity of the assessment. The results are considered robust if the modifications of the variables do not produce significant

changes in the outcome. The present authors elected to modify the variables that carried the greatest weight in the cost estimations. The calculation of cost-effectiveness was then repeated, substituting each one of the original values with the value derived from the extremes of the 95% CI.

RESULTS

The study included 271 patients. Table 1 summarises the demographic characteristics, initial severity of disease and clinical progress in the 190 patients of group A and the 81 patients of group NA. Nonadherent treatments were: second-generation cefalosporin±macrolide in 30 patients, macrolides in monotherapy in 19, ciprofloxacin±another antibiotic in 19, ceftazidime±another antibiotic in 10 and other regimens in three. There were no significant differences in demographic variables, comorbidity or initial severity. Overall mortality was 11% (30 out of 271), with 10% (19 out of 190) in group A *versus* 13.6% (11 out of 81) in group NA (p=0.3). The overall mean±SD duration of hospitalisation was 9.8±5.5 days: 9.7±5.2 in group A and 10.1±6.2 in group NA (p=0.7). Four patients (2%) in group A and 11 (6%) in group NA were readmitted within 30 days (p=0.1 and p>0.05, respectively).

TABLE 1 Demographic characteristics, comorbidity and initial risk class in the groups with and without treatment guidelines adherence (univariate analysis)

	Adherence to guidelines		p-value
	Yes	No	
Subjects n	190	81	
Sex male/female	82/108	28/53	0.1
Age yrs	69.4±15.6	72.3±14	0.1
Nursing home	5 (2.6)	3 (3.7)	0.6
Smoking habit	31 (16.3)	10 (12.1)	0.3
Hospitalisation during previous year	58 (30.5)	24 (29.6)	0.8
Prior antibiotic	71/190 (37.3)	25/81 (30.8)	0.3
Diabetes	40 (21.1)	17 (21)	0.9
Neoplasia	10 (5.3)	3 (3.7)	0.5
Liver disease	6 (3.2)	3 (3.7)	0.5
Heart failure	65 (34.2)	24 (29.6)	0.4
Cerebrovascular disease	21 (11.1)	10 (12.3)	0.7
Renal disease	12 (6.3)	4 (4.9)	0.6
COPD	42 (22.1)	27 (33.3)	0.06
Fine risk class			
I	19 (10)	3 (3.7)	0.09
II	23 (12.1)	13 (16)	
III	31 (16.3)	22 (27.2)	
IV	84 (44.2)	29 (35.8)	
V	33 (17.4)	14 (17.3)	

Data are presented as mean±SD or n (%), unless otherwise stated. COPD: chronic obstructive pulmonary disease.

Economic calculations: cost-minimisation and cost-effectiveness analysis

The mean cost of in-patient treatment for the whole cohort was 2,025±1.197 Euros. The mean cost for each component was: drug treatment 267±317 Euros, laboratory and diagnostic tests 353.9±297 Euros and hospital room 1,403±789 Euros. The separate results for groups are shown in table 2. Adherence resulted in better patient outcome (88% *versus* 81% cured patients) and at lower cost, although without reaching statistical significance (p>0.05). Two economic evaluation methods were performed: 1) a cost-minimisation analysis, since the difference in outcome between the two options was not found statistically significant; and 2) a cost-effectiveness analysis with a bootstrapping method, since the present study was not designed to show equivalence of treatments.

Cost-minimisation analysis

The incremental cost between the two options was 78.5 Euros (95% CI -261.7–418.7). Adherence to SEPAR guidelines saved 78.5 Euros per patient when compared with nonadherence.

Cost-effectiveness analysis

The cost-effectiveness ratio (C/E) or mean cost per patient cured was 2,277 Euros in group A and 2,567 Euros in group NA. The ICER was negative, which indicates that the treatment according to the guidelines had a saving of 1,121 Euros per cured patient compared with the alternative option of nonadherence. A bootstrapping nonparametric method was employed using 2,000 re-samples in order to perform a stochastic analysis. The ICER for this bootstrap re-sample was -942.7 Euros (95% CI -1,885.8–0.37). The ICER had values <1,256 Euros in 80% and <3,616 Euros in 90% of re-samples.

Sensitivity analysis

Three sensitivity analyses were performed with the different compartments of the total costs, including: antibiotics, hospital stay, laboratory tests and diagnostic evaluations. For each sensitivity analysis, all the costs were re-calculated using the extreme limits of the 95% CI of each compartment. For upper and lower limit of the 95% CI of the mean (table 3), the mean cost per patient in the two groups was re-calculated as well as the cost-effectiveness ratio and the incremental cost-effectiveness ratio.

The results (table 4) showed that the cost-effectiveness results remained stable despite being subjected to wide variations in the distinct cost components.

DISCUSSION

The most relevant results of the present study are: 1) adherence to guidelines is quite high; 2) adherence to guidelines in the empirical treatment of CAP is a dominant option since the outcomes are more effective compared with nonadherence (88% *versus* 81% cured patients) and less expensive (2,001 *versus* 2,079 Euros), as demonstrated by the cost-effectiveness analysis; 3) a cost-minimisation analysis showed that adherence to guidelines saved 78.5 Euros per patient; and 4) the incremental cost-effectiveness ratio showed that adherence to guidelines saved 1,121 Euros per patient cured compared with the nonadherence option.

TABLE 2 Cost results in the adherent and nonadherent group

	Adherence to guidelines		p-value
	Yes	No	
Overall treatment cost	257.9; 190.9 (113.6–303.3)	289.3; 181.1 (114.5–311.3)	0.8
Antibiotics	176.8; 139.3 (82.8–227.4)	170.8; 135.2 (73.6–236.8)	0.6
Other	80.3; 38.0 (14.9–68.3)	118.5; 37.7 (22.4–69.6)	0.3
Diagnostic/laboratory test	355.8; 291.5 (216.7–393.7)	349.2; 283.0 (213.5–391.0)	0.6
Hospital stay	1387.3; 1142.9 (857.2–1750.1)	1441.0; 1285.8 (857.2–1714.4)	0.7
Total costs	2001.1; 1665.5 (1294.8–2513.1)	2079.6; 1710.5 (1181.2–2366.7)	0.8

Data are presented as mean; median (25th–75th percentiles). Costs are provided in Euros.

Guidelines of scientific societies assist the attending physician in the selection of treatment and their objective is to improve the outcome. In the present study, adherence to Spanish guidelines was rather high (70%) and was similar to that described in the literature, although there is a wide variation among hospitals and physicians [20–22]. Several factors might explain noncompliance with guidelines: various specialists prescribing treatment in emergency rooms, the inertia of previous practice (>50% second-generation cefalosporin ± macrolide or macrolide alone) or different perception of the influence of the guidelines' benefit [23], although in the present study this interesting topic was not specifically investigated. No significant differences were found for the treatment of patients based on age, sex, comorbidity and initial severity.

The efficacy of adherence to initial empirical treatment guidelines has been evaluated for its impact on mortality, clinical response, duration of hospital stay and, less systematically, on cost [12, 14, 20]. There are several studies that found a lower mortality when treatment was compliant with guidelines [13, 14, 21, 24] and, furthermore, a more rapid clinical stability was achieved [25]. However, there remains a lack of studies performing a pharmacoeconomic evaluation focusing on costs [15, 26]. A cost-effectiveness analysis (CEA) is a useful tool when evaluating costs and outcomes with different treatment modalities. As such, it is ideal in the present context [27, 28] even when no statistically significant differences have been demonstrated in the current study. In fact, a CEA is considered an appropriate analysis when a lack of significance is found

TABLE 3 Mean values of the variables included in the sensitivity analysis

Variable	Mean	95% CI LL	95% CI UL
Antibiotic treatment			
Adherence	176.8	154.8	198.8
Nonadherence	170.8	137.8	203.8
Diagnostic/laboratory tests			
Adherence	355.8	310.5	401.3
Nonadherence	349.2	295.1	403.4
Hospital stay			
Adherence	1387.3	1281.1	1493.6
Nonadherence	1441.1	1243.7	1638.4

CI: confidence interval; LL: lower limit; UL: upper limit. Costs are provided in Euros.

TABLE 4 Results of cost-effectiveness and sensitivity analysis comparing adherence and nonadherence treatment groups

	C	E %	C/E	ICER	Result
Cohort analysis					
Adherence	2001	88	2276.7	-1121	Dominant
Nonadherence	2079	81	2566.6		
Sensitivity analysis 1					
Treatment					
95% CI LL					
Adherence	2251.7	88	2558.7	-3715	Dominant
Nonadherence	2511.8	81	3100.9		
95% CI UL					
Adherence	2301.8	88	2615.7	-4155.7	Dominant
Nonadherence	2592.7	81	3200.8		
Sensitivity analysis 2					
Diagnostics					
95% CI LL					
Adherence	2225.1	88	2528.5	-3724	Dominant
Nonadherence	2485.8	81	3068.8		
95% CI UL					
Adherence	2328.4	88	2645.9	-4147	Dominant
Nonadherence	2618.7	81	3232.9		
Sensitivity analysis 3					
Hospitalisation					
95% CI LL					
Adherence	2155.8	88	2449.7	-2.202	Dominant
Nonadherence	2310.1	81	2851.9		
95% CI UL					
Adherence	2397.6	88	2724.5	-5670	Dominant
Nonadherence	2794.5	81	3450.8		

Costs are provided in Euros. C: cost; E: effectiveness; C/E: cost-effectiveness ratio; ICER: incremental cost-effectiveness ratio (mean cost per additional patient cured); Dominant: lower cost and better outcomes; CI: confidence interval; LL: lower limit; UL: upper limit.

and the study was not designed to demonstrate equivalence [26]. Some previous studies about costs have been focused on strategies to decrease admissions to hospital due to CAP [29]. However, it has been reported that while a reduction in admissions was possible, there was an increase in subsequent readmissions and a lower satisfaction of the patients [30]. In that and other studies, the main goal had been to contain costs without compromising patient outcomes [31, 32]. These studies provide valuable information for clinical practice despite the fact that their objectives had focused on avoiding adverse effects, rather than on efficacy.

Although guidelines stress the importance of implementing and maintaining adherence to the recommendations, there has been a paucity of data published about their impact on the cost-effectiveness of the treatment. In nonhospitalised patients with CAP, GLEASON *et al.* [33] found that adherence to the American Thoracic Society guidelines was associated with a reduction of costs in patients <60 yrs of age and, conversely, with an increase in those of >60 yrs of age with comorbidities.

In the present study, it was decided to include all the components of hospital costs since the selection of antibiotics influences other prognostic variables, such as treatment failure and clinical stability, which are related to length of hospital stay. As a measure of effectiveness the recovery of pneumonia (defined as the patient surviving the episode of pneumonia and not needing readmission within 30 days of discharge) was used. These outcome indicators are universally applicable and are widely accepted [32, 34, 35].

ORRICK *et al.* [36] compared the cost of care for patients hospitalised with CAP. They found that the median cost of hospitalisation was higher when treatment was not compliant with guideline recommendations (US$ 3,085 *versus* US$ 2,047). However, the authors did not perform any cost-effectiveness analyses. Recently, BAUER *et al.* [37] reported that patients treated with moxifloxacin benefited from an earlier discharge, although direct costs and clinical efficacy were similar to other antibiotics.

In the present study it was found that adherence to the guidelines was the cost-effective option since the ratio was 2,277 Euros per expected cure *versus* 2,567 Euros in those with nonadherent treatments. This produced a negative incremental cost-effectiveness ratio since adherence saved 1,121 Euros per patient cured compared with nonadherence. A bootstrapping analysis demonstrated that in 95% of cases adherence to guidelines saves costs [19]. Furthermore, the additional cost of readmission was reduced when the treatment was adherent. The sensitivity analysis demonstrated that the results found in the cost-effectiveness analysis remain stable despite using wide variations in the different components introduced into the cost equations.

As a limitation of the present study it should be highlighted that there was no evaluation of the impact on indirect cost, such as patient-reported lost days of normal activity. Also, the present study was observational and nonrandomised. Furthermore, patients with admission to ICU were not included in the present study since it is one of the highest determinants of cost in CAP [37].

In summary, for patients hospitalised with community-acquired pneumonia, treatment according to the guidelines is the dominant alternative due to its cost-effectiveness.

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RESULTADOS

Los resultados obtenidos en los diferentes estudios que componen esta Tesis Doctoral, han permitido obtener los siguientes resultados:

ARTÍCULO 1: "Empiric treatment in hospitalized community-acquired pneumonia. Impact on mortality, length of stay and re-admission" ***(Respiratory Medicine,2007;101:1909-1915)***

Descripción de la cohorte

En nuestro estudio se incluyeron 425 pacientes: 229 (53.9%) fueron admitidos en un hospital terciario y 196 (46.1%) en hospitales generales. Los datos demográficos y características clínicas se muestran en la tabla 1. No hubo diferencias significativas entre los cuatro hospitales en términos de comorbilidad, edad y sexo. Sin embargo, el hábito tabáquico fue más frecuente en el Hospital C y D, p=0.02.

Regímenes antibióticos

Los regímenes antibióticos adherentes que se utilizaron fueron: beta-lactámico + macrólido (n=244, 57.4%), beta-lactámico en monoterapia (n=72, 16.9%), y quinolonas (n=11, 2.6%). Los tratamientos no adherentes se clasificaron como: macrólidos en monoterapia (n=32, 7.5%) y otros (n=66, 15.5%). En este último, se incluyeron cefalosporinas de segunda generación + macrólidos (n=33, 7.7%), ciprofloxacino en monoterapia (n=3, 0.7%), ciprofloxacino + macrólido (n=13, 3.2%) o más amoxicilina-clavulánico (n=1, 0.2%), cefalosporina de 3ª o 4ª generación + amikacina (n=5, 1.1%), imipenem (n=4, 0.9%), cefalosporina de 2ª generación en monoterapia (n=3, 0.7%), vancomicina más macrólido o cefalosporina antipseudomónica (n=3, 0.7%), piperacilina-tazobactam (n=1, 0.2%). La distribución por grupos en cada hospital se muestra en la Tabla 2.
El régimen terapéutico más utilizado en los cuatro hospitales fue la combinación de beta-lactámico y macrólidos. Sin embargo, el régimen fue menos utilizado en el Hospital B (38.5%), donde se determinó un incremento de la utilización de otros regímenes (31.5%), debido a una mayor prescripción de cefalosporinas de segunda generación + macrólidos.
La adherencia del tratamiento a las guías clínicas de la SEPAR para el global de la cohorte fue 76.5%. La adherencia fue diferente entre los hospitales, sin embargo, se observó más baja en el hospital B (53.4%) y C (67.2%) comparado con el hospital A (83.8%) y D (84.6%), p=0.0001. La distribución de los regímenes antibióticos según gravedad (Tabla 3) fue similar en el grupo de bajo y alto

riesgo, excepto para el grupo de macrólidos en monoterapia, el cual fue más frecuente en los pacientes de riesgo más bajo (13.6% versus 3.2%).

Mortalidad

La mortalidad global fue de 8.2%, sin existir diferencias significativas entre los hospitales estudiados. La mortalidad en el grupo adherente fue 26 (8.2%) y en el grupo no-adherente 9 (8.5%), p=0.9, y no existieron diferencias tras estratificar según la gravedad inicial. La mortalidad global para cada régimen antibiótico y de acuerdo con la gravedad se muestra en la Tabla 3. No hubo diferencias estadísticamente significativas en la mortalidad global cuando se observaron los diferentes regímenes de tratamiento. En el grupo de bajo riesgo, la mortalidad fue más elevada entre los pacientes tratados con beta-lactámicos en monoterapia (7.1%), aunque no fue estadísticamente significativo. En el grupo de riesgo elevado (clases Fine IV-V), la mortalidad fue mayor en el grupo de otros regímenes (24.3%), p=0.02.
Realizamos un análisis detallado de la mortalidad para cada régimen antibiótico (Figura 1). En esta figura hemos comparado los porcentajes de la mortalidad actual y predicha. La mortalidad real para todos los regímenes antibióticos fue más baja que el valor de la predicha, excepto para el grupo de otros antibióticos. En este último grupo, la mortalidad real fue mayor que la predicha según gravedad, con un incremento de muerte de un 30.2%.

Estancia Hospitalaria

La mediana de estancia hospitalaria fue de 8 días. No hubo diferencias entre el grupo adherente y no adherente, p=0.6.
En el análisis de la duración de la estancia por hospitales, encontramos estancias más cortas en el hospital D, con una mediana de 6 días, p=0.0001. No obtuvimos diferencias estadísticamente significativas en la duración de la estancia con respecto a los diferentes regímenes antibióticos utilizados y tampoco según gravedad inicial, p=0.4 (Tabla 3)

Reingreso

32 (7.6%) pacientes fueron readmitidos dentro de los 30 días tras el alta hospitalaria. El reingreso en el grupo adherente fue 25(7.9%), p=0.6. La distribución por hospitales fue: 17 pacientes en el Hospital A (7.5%), 6 en el hospital B (8.3%), 6 en el Hospital C (10.3%), y 3 pacientes en el hospital D (4.6%), p=0.6. No se encontraron diferencias estadísticamente significativas en el

reingreso con respecto al régimen de tratamiento utilizado. Sin embargo, la readmisión se relacionó con la gravedad inicial (2.1% en pacientes de riesgo bajo versus 5.4% en el grupo de riesgo elevado), aunque no se alcanzó la significación estadística (p=0.07) (tabla 3).

Análisis multivariado

Se realizaron tres análisis de regresión logística para predecir mortalidad, reingreso y estancia prolongada. Los factores de riesgo independientes para predecir mortalidad fueron escala de riesgo de Fine (OR=11.1, IC 95% 2.6-48.1), y el tratamiento con otros regímenes (OR=3, IC 95% 1.2-7.3). La monoterapia con beta-lactámicos fue factor de riesgo independiente para reingreso (OR=2.7, IC 95% 1.2-6.1), y en el tercer modelo, el ingreso en el hospital D fue factor protector para estancia prolongada (OR=0.2, IC 95% 0.1-0.5). (Tabla 4)

Tabla 1: Descripción del tratamiento empírico según edad, comorbilidad, estancia hospitalaria, mortalidad y reingreso.

	ADHERENCIA			NO ADHERENCIA		
	Beta-lactámico +macrólido	Beta-lactámico monoterapia	Quinolona	Macrólido monoterapia	Otros regimenes	p
Edad	70±16	73±14	72±18	55±21	70±16	0,008
Comorbilidad						
Cardiopatía	70 (28.7)	23 (31.9)	3 (27.3)	5 (15.6)	18 (27.3)	NS
EPOC	80 (32.8)	25 (34.7)	5 (45.5)	10 (31.3)	23 (34.8)	NS
Diabetes mellitus	50 (20.6)	16 (22.2)	0	1 (3.1)	18 (27.3)	NS
Cerebrovascular	37 (15.2)	10 (13.9)	3 (27.3)	3 (9.7)	10 (15.4)	NS
Nefropatía	16 (6.6)	5 (6.9)	0	0	2 (3.0)	NS
Hepatopatía	15 (6.1)	3 (4.7)	1 (9.1)	2 (6.3)	2 (3.0)	NS
Neoplasia	18 (7.4)	8 (11.1)	2 (18.2)	0	7 (10.6)	NS
Tabaco	45 (18.6)	6 (8.5)	2 (18.2)	15 (46.9)	9 (14.1)	NS
Asilo	10 (4.1)	1 (1.4)	1 (9.1)	0	6 (9.1)	NS
Estancia (días)	9±5	11±7	9±5	8±3	9±4	NS
Muerte	21 (8.6)	5 (6.9)	0	0	9 (13.6)	NS
Reingreso	15 (6.2)	10 (13.9)	0	3 (9.4)	4 (6.1)	NS
Hospital						
A	138 (60.3)*	48 (21.0)*	8 (3.5)*	9 (3.9)*	26 (11.4)*	
B	28 (38.4)	11 (15.1)	0	11 (15.1)	23 (31.5)	
C	30 (51.7)	9 (15.5)	0	8 (13.8)	11 (19.0)	
D	48 (73.8)	4 (6.2)	3 (4.6)	4 (6.2)	6 (9.2)	

*Comparación regímenes antibióticos entre los diferentes hospitales.
NS: no significativo; EPOC : enfermedad pulmonar obstructiva crónica

Tabla 2: Tratamiento antibiótico empírico según escala de riesgo de Fine.

Régimen antibiótico	FINE I-III N (%)	FINE IV-V N (%)	p
Beta-lactámico+ macrólido n=244 (57%)	91 (52)	153 (61)	0.04
Beta-lactámico monoterapia n=72 (17%)	28 (16)	44 (18)	0.6
Quinolona n=11 (2,6%)	4 (2)	7 (3)	0.7
Macrólido monoterapia n=32 (7,5%)	24 (14)	8 (3)	0.0001
Otros regímenes n=66 (15,5%)	29 (16)	37 (15)	0.6
Total	176 (100)	249 (100)	

Tabla 3: Descripción del tratamiento empírico inicial deacuerdo con la clase de riesgo.

Regimen antibiótico	**Mortalidad (n,%)**		**Estancia hospitalaria[a]** (mediana)		**Reingreso (n,%)[b]**	
	I-III*	IV-V	I-III	IV-V	I-III*	IV-V
Beta-lactámico+ macrólido	1(1.1)	20(13.1)	8	8	4(1.7)	11(4.5)
Beta-lactámico monoterapia	2(7.1)	3(6.8)	8	9	4(5.6)	6(8.3)
Quinolona	0	0	8	8	0	0
Macrólido monoterapia	0	0	8	8	1(3.1)	2(6.3)
Otros regímenes	0	9 (24.3)[c]	8	8	0	4(6.1)
Total	3(1.7)	32(12.9)	8	8	9(2.1)	23(5.4)

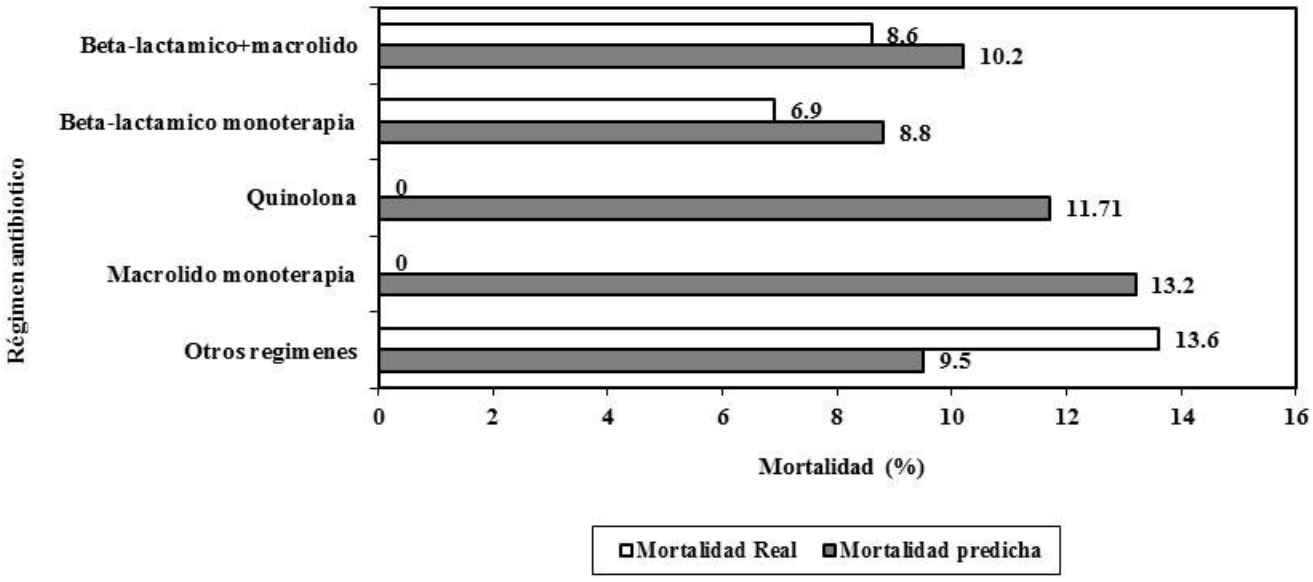
[a]p=0,4 Comparación mediana Estancia hospitalria en pacientes de riesgo bajo vs riesgo alto
[b]p=0,07Comparación reingreso pacientes de riesgo bajo 2.1% versus 5.4% en riesgo elevado
[c]p=0,02: en el grupo de riesgo elevado, la mortalidad fue más elevada en el grupo con otros regímenes de tratamiento (24,3%)

Tabla 4. Resultados del análisis de regresión logística para predecir mortalidad, reingreso y estancia hospitalaria prolongada.

	Mortalidad OR (95%CI)	Reingreso OR (95%CI)	Estancia prolongada OR (95%CI)
FINE(IV-V/I-III)	**11.1 (2.6-48.1)**	**NS**	**NS**
Adherencia	**NS**	**NS**	**NS**
Otros regímenes	**3 (1.2-7.3)**	**NS**	**NS**
Betalactámicos	**NS**	**2.7 (1.2-6.1)**	**NS**
Hospital A	**NS**	**NS**	**NS**
Hospital B	**NS**	**NS**	**NS**
Hospital C	**NS**	**NS**	**NS**
Hospital D	**NS**	**NS**	**0.2 (0.1-0.5)**

NS: no significativo
Variables dependientes: mortalidad, reingreso y estancia prolongada (>8 días)
Variables independientes: PSI (bajo y alto riesgo), hospital de ingreso (A,B,C,D), Tratamiento adherente (si/no) y régimen antibiótico empírico clasificado en: beta-lactámico en monoterapia, beta-lactámico más macrolidos, quinolonas, macrolido en monoterapia y otros regimenes

Gráfico 1: Mortalidad real y predicha para cada régimen antibiótico.



ARTÍCULO 2. "Determinants of hospital costs in community-acquired pneumonia" ***(European Respiratory Journal 2008;31:1061-1067)***

Población a estudio

Se incluyeron 271 pacientes hospitalizados por NAC. Las características demográficas, comorbilidad, gravedad inicial por escala de riesgo de Fine, complicaciones y mortalidad se describen en la Tabla 1.
El diagnóstico etiológico se alcanzó en 35 pacientes (12.9%); los microorganismos encontrados fueron: *S. pneumoniae* (n=22, 8.1%), *Enterococcus faecalis* (n=3, 1.1%), *Staphylococcus aureus* (n=2, 0.7%), *pseudomona aeruginosa* (n=2, 0.7%), *Haemophilus parainfluenzae* (n=2, 0.7%), *L. Pneumophila* (n=1, 0.4%), y otros microorganismos (n=4, 1.5%). Se detectó bacteriemia en 16(5.9%) pacientes. 203(74.9%) pacientes tenían comorbilidad asociada, de los cuales presentaban una única comorbilidad 122(45%) pacientes y dos o más comorbilidades en 81 (29.9%) pacientes. Aparecieron complicaciones en 196 (72.3%) pacientes. Las complicaciones se muestran en la tabla 1. Entre las complicaciones pulmonares, 100 (36.9%) presentaron insuficiencia respiratoria, y 42(17%) presentaron derrame pleural. Las complicaciones cardiovasculares fueron: fallo cardiaco congestivo 41 (15.1%) y shock cardiogénico 10 (3.7%); Complicaciones digestivas: alteraciones hepáticas 7 (2.6%), sangrado 6 (2.2%) y diarrea 9 (3.3%). Complicaciones infecciosas: infección nosocomial 6 (2.2%), empiema 5 (1.8%), meningitis 1, (0.4%) y endocarditis 1 (0.4%).

Resultados de costes

La mediana y rango intercuartil del coste total de la cohorte fue 1683 (1291-2471) €. La distribución de cada uno de los componentes fue la siguiente: duración de la estancia 1286 (857-1714) €, pruebas de laboratorio 212 (171-272) €, tratamiento 187(114-304) € : tratamiento antibiótico 138 (81-229)€ y otros tratamientos 38(17-68)€; pruebas diagnósticas 58 (29-122)€. El porcentaje del coste total correspondiente a cada componente fue: duración de la estancia hospitalaria (69.8%), tratamiento (13.1%), pruebas de laboratorio (11.9%) y pruebas diagnósticas (5.7%). La mediana del coste en pacientes con diagnóstico etiológico fue significativamente más elevada que en los pacientes con diagnóstico etiológico desconocido 2102 (1485-3485) € versus 1645 (1261-2286) €; p=0.01. De estos, los componentes, con mayor coste fueron: pruebas de laboratorio 265 (190-317) € vs 205 (168-262) €; p=0.001, pruebas diagnósticas 107 (42-234) € vs 53 (29-116) €; p=0.009, y duración de la estancia 1714 (1000-2000) € vs 1143 (857-1714) €;

p=0.01. No encontramos diferencias en los costes según microorganismo. Sin embargo, la mediana total del coste en pacientes con bacteraemia fue significativamente más elevada 2083 (1507-3775) €, que los no bacteriémicos 1628 (1231-2402) €; p=0.04. Cuando estos costes se desglosaron en sus componentes, los costes más elevados fueron los de laboratorio 256 (196-384) € vs 213 (175-271) €, p=0.049 y la duración de la estancia 1714 (1143-2429) vs 1143 (857-1714) €, p=0.03.

Los costes deacuerdo con la edad, sexo, vacunación antigripal, comorbilidades y complicaciones se describen en la table 2. Se registró una tendencia hacia el aumento de costes entre los pacientes mayores de 70 años de edad, aunque no se alcanzó la significación estadística. La vacunación contra el virus influenza no se relacionó significativamente con la gravedad inicial, la duración de la estancia o los costes. En los pacientes sin comorbilidad, el coste total promedio fue de 1631 (1304-2218) €, mientras que, en pacientes con una sola condición de comorbilidad, el coste fue de 1637 (1180-2320) €, y en aquellos con dos o más comorbilidades, fue 1771 (1386-2695) €; p = 0.03.

Los costes directos de acuerdo con la escala de gravedad de Fine se describen en la Tabla 3. Se observó una correlación positiva entre el coste total (rho = 0.15, p = 0.009), así como el coste de cada uno de los componentes, a excepción de las pruebas de diagnóstico y la escala de Fine, es decir, a mayor clase de riesgo, mayor coste.

El coste total medio de las neumonías sin complicaciones fue de 1295 (1055-1637) € frente a 1.692 (1392-2083) € en los pacientes con una sola complicación, y 2111 (1485-3007) € en pacientes con dos o más complicaciones; p = 0.0001 (Tabla 4). Las diferencias fueron significativas para cada uno de los componentes del coste. Los costes totales de acuerdo con el tipo de complicaciones se representan en la Tabla 2; las complicaciones infecciosas, renales y cardiovasculares tenían costes más elevados.

La mediana del coste total de los supervivientes fue 1690 (1294- 2313) €, y en los no supervivientes 1574 (978- 3476), p = 0.9. Hubo diferencias significativas en los siguientes componentes del coste entre los supervivientes y no supervivientes: coste del tratamiento 177 (113-281) € vs 353 (123-584) €; p = 0.004, en el tratamiento no antibiótico 33 (15-66) € vs 63 (23 a 271) €; p = 0,001 y en los costes de laboratorio 205 (168-265) vs 260 (204-298) €; p = 0,003. Sin embargo, no encontramos diferencias en el coste de la duración de la estancia, 1.286 (857-

1714) vs 1.000 (429-2.286) €; p = 0.1, aunque la duración de la estancia fue mayor para los supervivientes (mediana 9 días) que en los no supervivientes (mediana 7 días).

Factores relacionados con coste elevado

Análisis univariado.

La edad avanzada del paciente, el sexo, los hábitos tóxicos, el asilo y las comorbilidades no se asociaron significativamente con coste elevado en la NAC. En contraste, la hospitalización previa se asoció con un mayor coste (mediana 1624 € frente a 1888 €, p = 0.01). La gravedad inicial elevada también se asoció con alto coste (p = 0.01) (Tabla 3). Las alteraciones de laboratorio que se encuentran en pacientes con altos costes fueron: urea elevada (p = 0.01), hiperglucemia (p = 0.007), insuficiencia respiratoria (p = 0.002), y la hipoalbuminemia (p = 0.0001). La mediana del coste de todas las complicaciones (pulmonar, infecciosa, cardiovascular, digestivo, renal y otros) se asoció significativamente con alto coste, p = 0.0001

Análisis multivariado. Las siguientes variables independientes se incluyeron en el modelo, ya que resultaron significativas en el análisis univariado: la hospitalización previa, insuficiencia respiratoria, hipoalbuminemia, urea elevada, la hiperglucemia, gravedad inicial elevada y las complicaciones. La edad avanzada y las comorbilidades (no significativas) también fueron incluidos porque constituían uno de los objetivos de nuestro estudio. El modelo matemático seleccionado las siguientes variables asociadas con coste elevado (Tabla 5): complicaciones infecciosas, digestivas, pulmonares y otras complicaciones, hipoalbuminemia y admisión previa en el hospital.

Table 1. Características de la población a estudio

Edad (media ± DT)	70±15
Sexo (M/F)	161 (59.4) / 110 (40.6)
Fumador n (%)	41 (15.1)
Alcohol n (%)	41 (15.1)
Asilo n (%)	8 (3.0)
Comorbilidad n (%)	
Neoplasia	13 (4.8)
Hepatopatía	9 (3.3)
Cardiovascular	89 (32.8)
Cerebrovascular	31 (11.4)
Nefropatía	16 (5.9)
Diabetes	57 (21.0)
EPOC	69 (25.5)
Fine n (%)	
I	22 (8.1)
II	36 (13.3)
III	53 (19.6)
IV	113 (41.7)
V	47 (17.3)
Duración estancia (mediana)	9
Complicaciones n (%)	
Pulmonares	142 (52.4)
Renales	21 (7.7)
Cardiovascular	51 (18.8)
Digestivas	22 (8.1)
Infecciosas	13 (4.8)
Otras	55 (20.3)
Mortalidad n (%)	30 (11.1)

M: male; F: female; COPD: chronic obstructive pulmonary disease;

Tabla 2. Costes hospitalarios según edad y sexo, presencia de comorbilidades y complicaciones.

	Si	No	p*
Sexo (Hombre)	1636 (1177-2392)	1812 (1370-2533)	0.2
Edad ≤ 70 años	1548 (1178-2281)	1804 (1367-2548)	0.06
Vacunación antigripal	1796 (1371-2483)	1547 (1333-2786)	0.6
Comorbilidades			
Neoplasia	1291 (1030-2059)	1691 (1328-2513)	0.1
Hepatopatía	1426 (1173-2148)	1691 (1292-2504)	0.4
Cardiopatía	1700 (1343-2695)	1665 (1229-2292)	0.5
Sistema nervioso central	1833 (1291-2730)	1655 (1278-2354)	0.2
Nefropatía	1696 (1337-2433)	1674 (1273-2471)	0.7
Diabetes	1700 (1378-2715)	1665 (1271-2367)	0.4
EPOC	1771 (1320-2674)	1658 (1271-2274)	0.2
Complicaciones			
Respiratorias	1996 (1394-2843)	1485 (1122-1979)	0.001
Derrame pleural	2324 (1487-3321)	1630 (1250-2206)	0.001
Insuficiencia respiratoria	1846 (1380-2665)	1533 (1175-2140)	0.004
Infeccciones	2783 (2045-6161)	1645 (1271-2332)	0.005
Empiema	2075 (1531-2892)	1666 (1287-2427)	0.3
Infección nosocomial	3405 (1728-5716)	1659 (1282-2392)	0.06
Cardiovascular	2691 (1375-3485)	1634 (1261-2154)	0.002
Digestivas	2591 (1755-3807)	1634 (1263-2275)	0.002
Renales	2744 (1414-3616)	1655 (1271-2292)	0.04
Otras	2068 (1516-3607)	1620 (1182-2223)	0.0001

Resultados expresados en mediana (p25-p75) costes en €; * Mann-Whitney U-test.

Tabla 3. Costes directos y gravedad inicial (FINE)

Costes	FINE						
	I	II	III	IV	V	p*	Total
Medicamentos	187 (114-304)	116 (64-244)	121 (64-244)	181 (129-297)	194 (123-282)	262 (136-419)	0.001
ATB	138 (81-229)	109 (55-173	109 (54-216)	138 (95-237)	143 (76-213)	158 (100-290)	0.02
Otros ttos.	38 (17-68)	17 (4-37)	16 (7-37)	37 (21-62)	43 (20-75)	55 (23-148)	0.001
Laboratorio	212 (172-272)	190 (143-251)	173 (146-229)	196 (164-265)	219 (178-285)	232 (190-310)	0.001
Test diagnósticos	58 (29-122)	65 (36-199)	60 (33-162)	52 (24-101)	65 (33-122)	73 (22-118)	0.7
Estancia	1286 (857-1714)	1071 (571-1464)	1143 (750-1429)	1143 (857-1786)	1286 (857-1786)	1429 (857-2286)	0.02
Costes totales	1683 (1291-2471)	1531 (1130-2053)	1602 (1078-2048)	1630 (1341-2469)	1804 (1353-2507)	1972 (1231-3297)	0.0009

Resultados expresados en mediana (p25-p75) costes en €; *p: Correlación Spearman.

Tabla 4. Costes directos de la NAC de acuerdo con la presencia de complicaciones.

Costes	No complicada	1 complicación	≥2 complicaciones	p*
Medicación				
Tto. antibiótico	115 (64-155)	139 (90-222)	155 (87-290)	0.0001
Otros tratamientos	20 (8-39)	36 (18-56)	57 (23-130)	0.0001
Laboratorio	174 (153-212)	219 (178-277)	239 (189-310)	0.0001
Pruebas Diagnósticas	42 (22-69)	53 (19-84)	97 (33-218)	0.0001
Duración estancia	1000 (714-1286)	1286 (1000-1571)	1429 (1000-2286)	0.0001
Coste Total NAC	1295 (1055-1637)	1692 (1392-2083)	2111 (1485-3007)	0.0001

Resultados expresados en mediana (p25-p75) costes en €; * Kruskal-Wallis test

Tabla 5. Análisis de regresión logística: factores asociados con alto coste. (>mediana coste total de NAC: 1683€).

	OR (IC 95%)
Hospitalización previa	2.3 (1.2-4.3)
Hipoalbuminemia	2.0 (1.1-3.6)
Complicaciones infecciosas	6.8 (1.3-36)
Complicaciones digestivas	5.9 (1.5-22.8)
Complicaciones pulmonares	2.6 (1.4-4.7)
Otras complicaciones	3.9 (1.8-8.4)

ARTÍCULO 3. "Economic evaluation of adherence to treatment guidelines in nonintensive care pneumonia" ***(European Respiratory Journal 2007;29:751-756)***

En nuestro estudio se incluyeron 271 pacientes. En la tabla 1, se muestran las características demográficas, la severidad inicial y la progresión clínica de los pacientes del grupo adherente y del no adherente. Como podemos observar en la Tabla 1, no hubo diferencias significativas en las variables demográficas, comorbilidad o gravedad inicial.

La mortalidad global fue 11%, 10% en el grupo adherente frente a 13.6% en el grupo no adherente (p=0.3). La duración de la hospitalización fue de 9,8±5,5 días, en el grupo adherente 9,7±5,2 frente a 10,1±6,2 en el grupo no adherente p=0.1. En cuanto al reingreso, 2% en el grupo adherente vs 6% en el no adherente (p>0.05)

Cálculos económicos: minimización de coste y análisis coste-efectividad

Entre los resultados del cálculo económico, la media del coste para cada componente fue: coste tratamiento: 267±317 €, coste pruebas diagnósticas y laboratorio 353,9±297€, estancia hospitalaria 1403±789€.

En la siguiente Tabla 2 se muestran los costes separados según adherencia o no al tratamiento. La adherencia al tratamiento resultó la mejor opción para el paciente en cuanto a resultados (88% vs 81% pacientes curados) y menor coste, aunque sin alcanzar diferencias estadísticas significativas (p>0.05).

En nuestro estudio se realizaron dos métodos de evaluación económica: 1ª análisis de minimización de costes, ya que la diferencia en los resultados entre las dos opciones no se encontró estadísticamente significativa; y 2ª un análisis de coste efectividad con un método de bootstrapping, ya que este estudio no fue diseñado para mostrar la equivalencia de los tratamientos.

Análisis de minimización de costes:

El coste incremental entre las dos opciones fue de 78,5 euros (CI 95% -261,7-418,7). La adherencia a normativas SEPAR ahorró 78,5 euros por paciente en comparación con el tratamiento no adherente.

Análisis de coste efectividad:

La relación coste-efectividad (C / E) o media del coste por paciente curado fue 2277 € en el grupo adherente y 2.567 € en el grupo no adherente. La relación

coste-efectividad incremental (ICER) fue negativa, lo que indica que el tratamiento de acuerdo con las directrices tiene un ahorro de 1.121 euros por paciente curado en comparación con la opción alternativa de la no adherencia. Utilizamos un método no paramétrico de bootstrapping usando 2000 re-muestras con el fin de realizar un análisis estocástico.

El ICER para este bootstrap fue -942.7 euros (IC del 95% -1885.8-0.37). El ICER tuvo valores <1256 euros en 80% y < 3616 euros en el 90% de las remuestras.

Análisis de sensibilidad:

Se realizaron tres análisis de sensibilidad con los diferentes componentes de los costes totales, incluyendo: antibióticos, estancia hospitalaria, pruebas de laboratorio y diagnósticos. Para cada análisis de sensibilidad, todos los costes fueron re-calculados utilizando los límites extremos del IC del 95% de cada componente. Para el límite superior e inferior del IC del 95% de la media (tabla 3), la media-coste por paciente en los dos grupos fue recalculado, así como la relación coste-efectividad y la relación coste-efectividad incremental. Los resultados (tabla 4) muestran que los resultados de coste-efectividad permanecen estables a pesar de ser sometido a grandes variaciones en los diferentes componentes de los costes.

Tabla 1. Características demográficas, comorbilidad y clase de riesgo inicial en los grupos de tratamiento adherente/no adherente a las guías clínicas

		Adherencia guías clínicas		P
		Si N = 190 (%)	No; N = 81 (%)	
Sexo; M/F		82/108	28/53	0.1
Edad; años		69.4±15.6	72.3±14	0.1
Asilo		5(2.6)	3(3.7)	0.6
Tabaco		31(16.3)	10(12.1)	0.3
Hospitalización año previo		58 (30.5)	24(29.6)	0.8
Antibiótico previo		71/190(37.3)	25/81(30.8)	0.3
Diabetes		40(21.1)	17(21)	0.9
Neoplasia		10(5.3)	3(3.7)	0.5
Hepatopatía		6(3.2)	3(3.7)	0.5
Insuficiencia cardiaca		65(34.2)	24(29.6)	0.4
Enfermedad cerebrovascular		21(11.1)	10(12.3)	0.7
Enfermedad Renal		12(6.3)	4(4.9)	0.6
EPOC		42(22.1)	27(33.3)	0.06
FINE				
	I	19 (10)	3(3.7)	0.09
	II	23(12.1)	13(16)	
	III	31(16.3)	22(27.2)	
	IV	84(44.2)	29(35.8)	
	V	33(17.4)	14(17.3)	

Datos en media±desviación típica o n(%)

Tabla 2. Resultados de costes en los grupos adherente/no adherente

	Adherencia a las guías clínicas Media Mediana (p25-p75)		p
	Si	No	
Coste tratamiento (total)	257.9 190.9(113.6-303.3)	289.3 181.1(114.5-311.3)	0.8
Antibióticos	176.8 139.3(82.8-227.4)	170.8 135.2(73.6-236.8)	0.6
Otros	80.3 38.0(14.9-68.3)	118.5 37.7(22.4-69.6)	0.3
Test diagnóstico/laboratorio	355.8 291.5(216.7-393.7)	349.2 283.0(213.5-391.0)	0.6
Estancia hospitalaria	1387.3 1142.9(857.2-1750.1)	1441 1285.8(857.2-1714.4)	0.7
Coste Total	2001.1 1665.5 (1294.8-2513.1)	2.079.6 1710.5(1181.2-2366.7)	0.8

Tabla 3. Valores medios de las variables incluidas en el análisis de sensibilidad.

Variable	Media	IC 95% Límite inferior	IC 95% Límite superior
Tratamiento antibiótico			
Adherencia	176.8	154.8	198.8
No adherencia	170.8	137.8	203.8
Test diagnósticos/laboratorio			
Adherencia	355.8	310.5	401.3
No adherencia	349.2	295.1	403.4
Estancia hospitalaria			
Adherencia	1387.3	1281.1	1493.6
No adherencia	1441.1	1243.7	1638.4

Tabla 4. Resultados del análisis coste-efectividad y sensibilidad comparando el grupo de tratamiento adherente/no adherente.

	Coste	Efectividad (%)	C/E	ICER	Resultado
Análisis cohorte					
Adh/ No adh	2.001/2.079	88/81	2276.7/2566.6	-1121	Dominante
Análisis sensibilidad 1					
Tratamiento					
IC 95% L.inf (Adh/no Adh)	2.251.7/2.511.8	88/81	2.558.7/3.100.9	-3715	Dominante
IC 95%; L.sup(Adh/no Adh)	2.301.8/2.592.7	88/81	2.615.7/3200.8	-4155.7	Dominante
Análisis sensitibilidad 2					
Diagnosticos					
IC 95%; L.inf(Adh/no Adh)	2225.1/2485.8	88/81	2528.5/3068.8	-3724	Dominante
IC 95%; L.sup(Adh/no Adh)	2328.4/2618.7	88/81	2645.9/3232.9	-4147	Dominante
Análisis sensitibilidad 3					
Hospitalización					
IC 95%; L.inf(Adh/no Adh)	2155.8/2310.1	88/81	2449.7/2851.9	-2.202	Dominante
IC 95%; L.sup(Adh/no Adh)	2397.6/2794.5	88/81	2724.5/3450.8	-5670	Dominante

Dominante: menor coste y mejores resultados.

DISCUSION

El proceso de investigación en la presente Tesis se consideran el punto de partida para iniciar la discusión sobre el alcance de los resultados de los trabajos presentados en esta investigación.

ESTUDIO 1

Las características de la población de este estudio fueron similares en los cuatro hospitales analizados y semejante a los estudios de NAC hospitalizada. La elección del tratamiento empírico se realizó según las normativas SEPAR [20, 21] en un porcentaje elevado de pacientes 76.5%, con diferente grado de adherencia entre los cuatro hospitales. Los resultados globales mostraron que la pauta utilizada con más frecuencia era la que incluía un beta-láctamico más un macrólido, este hallazgo se confirma en estudios realizados previamente nacionales e internacionales [22] [15], pero destaca que en un 9-31% se emplearon pautas o regímenes con antibióticos diferentes a los recomendados por las normativas. Así, en el hospital B, se instauraron más otros regímenes antibióticos, debido a una mayor utilización de cefalosporinas de 2ª generación más macrólidos, que aunque no se adhiere a la normativa SEPAR, por el contrario sí que sigue la normativa americana [23]. La distribución de las pautas antibióticas según clase de riesgo inicial fue similar tanto para clases de riesgo bajo como alto, excepto una mayor utilización de macrólidos en monoterapia en pacientes menos graves.

La mortalidad encontrada en nuestro estudio (8,2%) fue similar a la encontrada por otros autores [24-27] y se ajustó a la clase de riesgo de Fine. Como hallazgo destacable encontramos que la mortalidad fue superior, sin alcanzar la significación estadística, en pacientes tratados con pautas no adherentes. Este hallazgo es más evidente en los pacientes con Fine V (38.5% versus 18.2%). Otros autores ya habían constatado menor mortalidad cuando el tratamiento se adhería a las normativas [15, 28, 29].

El análisis pormenorizado de las pautas antibióticas empleadas en nuestro estudio, muestran de forma global que la mortalidad fue superior en los pacientes tratados con pautas no habituales (13,6% vs 8,2%). Cuando se analiza en el grupo de pacientes graves, la mortalidad en los tratados con pautas no frecuentes aumenta de forma significativa (24,3% vs 6,8% y 13,1%). De hecho, la diferencia encontrada para cada pauta antibiótica entre la mortalidad real en el estudio y la esperada por clase de riesgo (gráfico 1), evidencia el incremento de muerte para este mismo grupo. Lo contrario sucedió con el resto de pautas

antibióticas, donde la mortalidad real fue menor. En este sentido otros autores [28] [8] [30], también encontraron mayor mortalidad en el grupo de enfermos tratados con pautas no habituales.

En el análisis multivariado para predecir mortalidad tras ajustar por Fine, se confirma que las pautas no habituales tienen una tendencia a mayor mortalidad con una OR 3 IC 95% (1.2-7.3).

En los pacientes de bajo riesgo, la mortalidad en los tratados con macrólidos y quinolonas en monoterapia fue inferior a la de los tratados con beta-lactámicos en monoterapia. Sin embargo, estos hallazgos hay que interpretarlos con cautela dado el escaso número de enfermos tratados con esta pauta y la escasa mortalidad propia de estas clases de riesgo.

La duración de la estancia hospitalaria no mostró diferencias significativas para las distintas pautas antibióticas, de hecho, tuvo más influencia el hospital donde ingresó el paciente. La duración fue menor en el hospital D y tampoco se relacionó con la adherencia o no a las normativas o con el uso de macrólidos. Algunos investigadores [31] [32] [33], encontraron menores estancias hospitalarias en pacientes tratados con macrólidos, pero no todos los autores coinciden en estos hallazgos [34] y posiblemente la duración de la hospitalización depende más de factores del propio paciente y del hospital [35-37]. Una guía clínica es buena cuando produce una reducción de consumo de recursos y de la duración de estancia hospitalaria sin causar efectos adversos en la mortalidad o en los reingresos. [38]

El reingreso de forma global fue de 7,6% y mostró tendencia a ser más elevado en los tratados con beta-lactámico en monoterapia y sobre todo en las neumonías graves (IV y V). En el estudio multivariado se encontró que, de forma independiente, el tratamiento beta-lactámico en monoterapia, fue un factor de riesgo de reingreso (OR 2,4). No existen apenas datos en la literatura referentes al reingreso en la NAC y las distintas pautas antibióticas [39] .

En conclusión, existe una alta adherencia a las normativas de tratamiento en la NAC hospitalizada, pero existe una amplia variabilidad de pautas antibióticas empíricas que se utilizan en la práctica clínica diaria. El empleo de pautas no adherentes se asocia con mayor tendencia de muerte en la NAC grave. Existen algunas pautas antibióticas que se asocian a menor porcentaje de reingreso sin influir apenas en la duración de la estancia hospitalaria. Los beta-

lactámicos se asociaron a mayor reingreso, aunque se necesitan más estudios para confirmar este suceso.

ESTUDIO 2

Los costes anuales de la neumonía han sido estimados por la Sociedad Respiratoria Europea en 10,1€ billones en Europa. De estos, 5,7€ billones corresponden al coste de pacientes hospitalizados por NAC [3]. En España, Monge y sus colaboradores [40, 41] registraron 53000 hospitalizaciones al año con un coste sanitario anual de 115€ millones. En este estudio, los costes documentados fueron ligeramente superiores a los registrados en la literatura nacional y europea. En otros estudios realizados en España, los costes directos de pacientes hospitalizados fueron 1210€ [42] y 1553€ [43]. En Europa, los costes directos oscilaron entre 1333€ en Alemania [44], hasta 2550€-7650€ en el Reino Unido [45]. Sin embargo, los coste europeos fueron significativamente más bajos que los registrados en EEUU, a pesar de medias de estancias hospitalarias más largas [11, 46] [47]. En un estudio prospectivo de 4 hospitales de EEUU, Fine et al., [11] determinó un coste total medio de 4468€ en pacientes hospitalizados por NAC.

La decisión de hospitalización depende de muchos factores, como la gravedad inicial, las comorbilidades y las complicaciones. En sujetos de edad avanzada, la hospitalización se decide en base a comorbilidad asociada y complicaciones, ambos factores son muy frecuentes en este grupo de población [47, 48] [10]. Sin embargo, en los jóvenes adultos, la mayor probabilidad de ingreso hospitalario se determina por la presencia de complicaciones graves y en menor medida por las comorbilidades [48, 49].

La contribución de cada uno de estos factores, comorbilidad, gravedad inicial y complicaciones en los costes totales de la NAC hospitalizada no han sido estudiados de forma extensa, aunque existen algunos estudios previos que han analizado el efecto de la edad del paciente. Así, Bartolomé y cols [43] encontraron costes significativamente más altos en pacientes de edad ≥ 65 años aunque no se detalla ni el impacto de la gravedad o de la enfermedad asociada. Asimismo, Niederman y cols [10] encontraron costes más elevados en pacientes >65 años 305$ millones versus 192$ millones en <65años. Esta diferencia en el coste fue fundamentalmente atribuible al mayor porcentaje de hospitalizaciones y a estancias hospitalarias más prolongadas en pacientes ancianos. Sin embargo, el impacto de la comorbilidad en el coste solo se confirmó en aquellos pacientes que requirieron servicios respiratorios, posiblemente en relación con estancias

hospitalarias prolongadas. Mientras que los resultados de nuestro estudio muestran una tendencia hacia el incremento del coste en pacientes mayores de 70 años, la diferencias no alcanzaron la significación estadística, y la edad no fue seleccionada como variable independiente en el análisis multivariado. Además, la presencia de dos o más comorbilidades no causó un aumento significativo de los costes hospitalarios

En el presente estudio, obtuvimos un incremento en los costes en pacientes con NAC más severa y que cursaron con más complicaciones. Bauer et al [44] demostró costes más elevados en pacientes con neumonías más severas, que requirieron ingreso en UCI comparado con pacientes con neumonías menos graves, debido sobre todo a estancias hospitalarias más prolongadas (2300$ versus 1242$); $p<0.0001$). Kaplan et al [48], también encontró pacientes con NAC complicada (con ingreso en UCI o necesidad de ventilación mecánica) con estancias hospitalarias más prolongadas e incremento en los costes comparados con los pacientes con neumonías no complicadas (8725$ versus 3754$). Aunque nuestro estudio no incluyó pacientes que requirieron UCI, en pacientes con mayor puntuación en la escala de riesgo de Fine obtuvimos costes más elevados debido a mayor número de estudios solicitados y mayor estancia hospitalaria. Kaplan et al [48] también encontró que en pacientes >65 años y comorbilidad asociada presentaban más complicaciones. Sin embargo, estos hallazgos también se explican por el hecho de que el PSI era mayor en este grupo.

El porcentaje de las neumonías complicadas en nuestra cohorte fue elevado (72,3%), aunque similar a las cifras reportadas en la literatura. [50] Las complicaciones infecciosas fueron las que ocasionaron mayores costes directos totales, sobretodo la infección nosocomial (3405€). Es bien conocido que, aunque la incidencia de la infección nosocomial es baja en la NAC, es una causa de fracaso del tratamiento y empeora seriamente el pronóstico [51]. Los presentes autores encontraron esta complicación como causa de coste elevado de hasta seis veces, debido a la necesidad de más pruebas, tratamientos, y sobre todo, debido a la prolongación de LOS [52].

Sin embargo, el impacto global de las complicaciones pulmonares, cardiacas y renales sobre el coste global de la NAC fue elevado, ya que produjeron un incremento significativo en los costes, y sobretodo porque su incidencia fue mucho mayor. Por otra parte, no fue raro encontrar más de una complicación, una condición que a su vez generó un aumento del coste.

El análisis multivariado confirmó que las complicaciones infecciosas (OR 6.8), digestivas (OR 5.9), pulmonar (OR 2.6) y otras complicaciones (OR 3,9) fueron los factores de riesgo independientes más fuertes para coste elevado. Además, otras dos variables con efectos independientes fueron identificadas en el modelo matemático: hipoalbuminemia (OR 2,0) y la hospitalización previa (OR 2,3). La hipoalbuminemia se asocia con neumonías más severas, y es más frecuente en ancianos.

Esto contribuye a una respuesta clínica más lenta al tratamiento y peor pronóstico. [36, 53] Cabré et al [54] encontraron que la hospitalización previa era un factor predictor de mala evolución en el paciente e incremento de la mortalidad a los 30 días. Una posible explicación para esto es que la hospitalización previa es más frecuente en pacientes ancianos [55]. La edad avanzada les predispone a condiciones más serias, la aparición de complicaciones y mayor mortalidad [6, 54, 56]. Sin embargo, la literatura existente no muestra una relación directa entre hospitalización previa, y costes hospitalarios, aunque todos estos factores producen un incremento total del coste de la NAC. Curiosamente, ni la edad ni la comorbilidad se asoció de forma independiente con un incremento del coste en el paciente hospitalizado. Observaciones similares se aplican al PSI, efecto que también desapareció en el análisis multivariado. Por lo tanto, el coste hospitalario de la NAC no fue significativamente mayor en pacientes con comorbilidades, o con PSI elevado, si no tenían complicaciones asociadas.

En conclusión, las complicaciones, la hipoalbuminemia y la hospitalización previa fueron los determinantes más importantes de alto coste asociada a pacientes hospitalizados por NAC. Sin embargo, ni la edad ni las comorbilidades contribuyeron a elevar los costes directos. La gravedad inicial (Fine) por sí sola no fue factor de riego independiente para alto coste tampoco. Estrategias diseñadas para prevenir complicaciones durante la estancia hospitalaria, y un tratamiento precoz de las complicaciones que aparezcan, podría contribuir a reducir los costes intrahospitalarios de la NAC.

ESTUDIO 3

Las directrices de las sociedades científicas ayudan al médico en la selección del tratamiento y su objetivo es mejorar los resultados. En el presente

estudio, la adherencia a las directrices españolas fue bastante alta (70%) y similar a la descrita en la literatura, aunque hay una amplia variación entre los hospitales y médicos [29, 57, 58]. Existen varios factores que podrían explicar el incumplimiento de las directrices: varios especialistas prescriben el tratamiento en los servicios de urgencias, la inercia de la práctica anterior (>50% cefalosporinas segunda generación +/- macrólido o macrólido en monoterapia) o diferente percepción de la influencia beneficiosa de las directrices [59], aunque en el presente estudio este interesante tema no ha sido específicamente investigado. No se encontraron diferencias significativas para el tratamiento de los pacientes según la edad, el sexo, la comorbilidad y gravedad inicial.

La eficacia de la adherencia a las guías en el tratamiento empírico inicial ha sido evaluada por su impacto en la mortalidad, respuesta clínica, duración de la estancia hospitalaria y, menos sistemática, en los costes [15, 29, 60]. Existen varios estudios que han encontrado una menor mortalidad cuando el tratamiento es adherente a las directrices [8, 28, 57, 60] y, además, una estabilidad clínica más rápida [52]. Sin embargo, sigue existiendo una falta de estudios que analicen una evaluación fármacoeconómica centrándose en los costes [21] [61].

Un análisis de costo-efectividad (CEA) es una herramienta útil cuando evaluamos costes y resultados con diferentes modalidades de tratamiento. Como tal, es ideal en el contexto actual [62, 63], incluso cuando no hay diferencias estadísticamente significativas como se ha demostrado en este estudio. De hecho, un análisis coste- efectividad se considera un análisis adecuado cuando se encuentra una falta de significación y el estudio no fue diseñado para demostrar la equivalencia [61]. Algunos estudios anteriores sobre costes se han centrado en estrategias para disminuir los ingresos hospitalarios por NAC [38]. Sin embargo, se ha demostrado que una reducción de los ingresos hospitalarios es posible, aunque posteriormente hubo un aumento de readmisiones posteriores y una menor satisfacción de los pacientes [64]. En ese y otros estudios, el objetivo principal ha sido contener los costes sin comprometer los resultados del paciente [65, 66]. Estos estudios proporcionan información valiosa para la práctica clínica a pesar de que sus objetivos se han centrado en evitar efectos adversos, más que en la eficacia.

Aunque las directrices hacen hincapié en la importancia de implementar y mantener la adherencia a las recomendaciones, se ha producido una escasez de datos publicados sobre su impacto en el coste-efectividad del tratamiento. En

pacientes no hospitalizados con NAC, Gleason et al, [67] encontraron que la adhesión a las directrices de la American Thoracic Society se asoció con una reducción de los costes en los pacientes < 60 años de edad y, a la inversa, con un aumento en los > 60 años de edad con comorbilidades.

En el presente estudio, se decidió incluir todos los componentes de los costes hospitalarios desde la influencia de la selección de antibióticos en otras variables pronósticas, como el fracaso del tratamiento y la estabilidad clínica, que están relacionados con la duración de la estancia hospitalaria. Como medida de efectividad se utilizó la curación de la neumonía (definido como el paciente que sobrevive al episodio de neumonía y no presenta readmisión dentro de los 30 días del alta). Estos indicadores de resultados son de aplicación universal y son ampliamente aceptadas [66, 68, 69].

ORRICK et al. [19] compararon el coste de los cuidados de los pacientes hospitalizados con NAC. Determinaron que el coste promedio de hospitalización fue mayor cuando el tratamiento no seguía las recomendaciones de las guías (US $ 3.085 frente a US $ 2.047). Sin embargo, los autores no realizaron ningún análisis de coste-efectividad. Recientemente, BAUER et al. [44] encontró que los pacientes tratados con moxifloxacino se beneficiaron de un alta precoz, aunque los costes directos y eficacia clínica fueron similares a otros antibióticos.

En el presente estudio encontramos que la adherencia a las directrices fue la opción más coste-efectiva ya que la relación fue 2.277 euros por curación esperada frente a 2.567 euros en los tratamientos no adherentes. Esto produjo un incremento negativo de la relación coste-efectividad ya que la adherencia ahorró 1.121 Euros por paciente curado en comparación con la no adherencia.

Un análisis bootstraping, demostró que en el 95% de los casos la adherencia a las directrices ahorra costes [70]. Por otra parte, el coste adicional de readmisión se redujo cuando el tratamiento era adherente. El análisis de sensibilidad demostró que los resultados encontrados en el análisis de costo-efectividad se mantienen estables a pesar de usar amplias variaciones en los diferentes componentes introducidos en las ecuaciones de costes.

Como limitación del estudio cabe destacar que no se ha realizado ningún análisis del impacto de los costes indirectos, tales como la pérdida de días de actividad laboral de los pacientes. Además, el presente estudio fue

observacional, no aleatorio. Por otra parte, los pacientes de UCI no fueron incluidos en el presente estudio, ya que es uno de los más altos determinantes del coste de la NAC [44].

En resumen, para los pacientes hospitalizados por neumonía adquirida en la comunidad, el tratamiento de acuerdo con las guías clínicas es la alternativa dominante debido a su coste-efectividad.

CONCLUSIONES

Las conclusiones de esta tesis responden a los objetivos que motivaron la investigación.

Estudio 1:

1) El régimen antibiótico más utilizado fue la asociación betalactámico más macrólido con una adherencia a las normativas del 76.5% y heterogeneidad entre los hospitales.
2) Los pacientes graves tratados con regímenes antibióticos no habituales/adherentes tienen un mayor riesgo de muerte
3) La monoterapia con betalactámicos se asoció con mayor porcentaje de reingresos.
4) No encontramos asociación entre pautas antibióticas y duración de la estancia hospitalaria.

Estudio 2:

1) La mediana del coste total en pacientes hospitalizados por NAC fue de 1683€ siendo la estancia el coste directo más alto
2) Las complicaciones incrementan de forma significativa e independiente el coste de la hospitalización siendo las infecciosas las de mayor coste.
3) Ni la edad del paciente ni las comorbilidades se asociaron de forma independiente con alto coste.
4) La hospitalización previa en el último año, la hipoalbuminemia son factores predictivos de coste elevado

Estudio 3:

1) La adherencia a las guías clínicas fue elevada en nuestro estudio.
2) El análisis coste-efectividad demuestra que la adherencia a las normativas en el tratamiento empírico de la NAC fue la opción dominante con resultados más eficaces en comparación con la no adherencia (88% versus 81% de los pacientes curados) y menos costosas (2,001versus 2.079 euros).
3) El análisis de minimización de costes mostró que la adherencia a las normativas ahorra 78,5 euros por paciente.
4) La ratio incremental costo-efectividad demostró un ahorro de 1.121 euros por paciente curado comparado con la opción de la no adherencia.

Conclusión final

Los resultados de la presente tesis suponen una aportación desde el punto de vista clínico a la búsqueda de medidas eficaces en el tratamiento de pacientes con NAC y como consecuencia en la calidad asistencial. Este estudio ha ayudado a demostrar la eficacia de las normativas SEPAR en términos de mejora de calidad asistencial y pronóstico. Ha ayudado a demostrar la eficacia en términos de coste-efectividad de las diferentes alternativas de tratamiento según la adherencia a las directrices y como consecuencia una reducción de los costes hospitalarios.

PUBLICACIONES RELACIONADAS

Relacionado con los trabajos que forman la presente Tesis Doctoral, se ha publicado también el siguiente artículo:

Menéndez R, Cremades MJ, Martínez Moragón E, Soler JJ, Reyes S, Perpiñá M. Duration of length of stay in pneumonia: influence of clinical factors and hospital type. *Eur Respir J* 2003;22:643-648.

(Factor de Impacto= 7,636)

Eur Respir J 2003; 22: 643–648
DOI: 10.1183/09031936.03.00026103
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European Respiratory Journal
ISSN 0903-1936

Duration of length of stay in pneumonia: influence of clinical factors and hospital type

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Duration of length of stay in pneumonia: influence of clinical factors and hospital type. R. Menéndez, M.J. Cremades, E. Martínez-Moragón, J.J. Soler, S. Reyes, M. Perpiñá. ©ERS Journals Ltd 2003.

ABSTRACT: Length of stay (LOS) in hospital for community-acquired pneumonia depends on the characteristics of the patient and hospital. The present study sought to identify these variables within the first 24 h of hospitalisation.

Patients hospitalised for pneumonia in four hospitals (one teaching and three general hospitals) had their data analysed by univariate and multivariate statististics. The variables entered were LOS, demographical characteristics, referral source, comorbidity, initial severity of illness, laboratory analyses, initial radiograph findings and antibiotic treatment regimens.

The study sample included 425 patients. The overall mortality was 8.2% and the median LOS was 9 days. Using LOS as a dependent variable, three multivariate linear regression analyses were performed with: 1) the whole cohort; 2) the low-risk classes (categories I and II of Fine); and 3) the high-risk classes (categories III, IV and V of Fine). The mathematical model identified hypoxemia, low diastolic pressure, pleural effusion, multi-lobe involvement and hypoalbuminaemia as associated with longer stays in risk classes III–V, while in the low-risk patients (I–II) only hypoxemia and pleural effusion appeared in the equation. Following adjustment for these clinical variables, the LOS remained lower in some hospitals.

Several independent clinical factors increased the pneumonia-associated length of stay with significant differences between hospitals. Hypoxemia and pleural effusions were the predictive variables of length of stay in low-risk patients and, additionally, diastolic blood pressure, multi-lobe involvement and hypoalbuminaemia were significant in the higher-risk classes III–V.

Eur Respir J 2003; 22: 643–648.

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Keywords: Community-acquired pneumonia
hospitalisation
length of stay
mortality
multiple linear analysis

Received: March 8 2003
Accepted after revision: May 15 2003

This work has been supported in part by Red Respira (RTIC C03/11).

Community-acquired pneumonia (CAP) is the cause of hospitalisation for 3–5 per 1000 adults per year and with a mortality rate of 5–15%. Pneumonia is the infectious disease with the highest health costs [1–4] and, since approximately one-third of all patients with CAP are treated in hospital, the resulting costs constitute a significant part of the overall direct costs of infectious diseases [5–7]. The most important component of these costs is the length of stay (LOS) in hospital and estimates indicate these costs to be higher than those of the diagnostic tests involved and the subsequent antimicrobial treatments administered [6].

There is considerable variability in LOS between hospitals. Reported findings are discordant and depend on the types of hospital in which the different studies had been conducted [8–11]. The differences might reflect variations in clinical practice preferences, hospital characteristics and patient characteristics and attitudes. Over recent years the LOS appears to have decreased from 9 to 6 days [12, 13] as a result of several strategies and practical guidelines that have been proposed in order to safely reduce the number of hospitalisation days [14].

The LOS is influenced by several clinical factors, such as the Pneumonia Severity Index (PSI) [15] associated comorbidity, and the presence of clinical complications. These factors have been evaluated in recent reports [9, 11, 16, 17], but to-date, there has been no clear identification of the variables that determine LOS using the methods of multivariate analyses with adjustment for confounding variables. Neither have there been any studies on the possible differences in LOS between patients admitted to hospital with different grades of seriousness of the illness. Published studies have indicated that a substantial percentage of hospitalisations are comprised of patients of risk classes I–II that, despite the low probability of death ensuing if treated on an outpatient basis, nevertheless could benefit more from hospitalised treatment.

The hypothesis of the current study was that LOS is not influenced by identical variables affecting patients with different grades of initial severity of illness and that the type of admitting hospital has an influence. Hence, the objective of the present study was to identify, during the first 24 h following admission, the clinical factors associated with the duration of hospitalisation for CAP in patients with different grades of illness on admission (risk classes I and II *versus* risk classes III–IV and V). Identification of independent predictive factors of LOS would help clinicians to evaluate the need for, and the duration of, hospitalisation for community acquired pneumonia and to rationalise the patient's discharge from hospital.

Patients and methods

Study subjects

A prospective follow-up study was performed in four public hospitals, of which three are general urban hospitals of

different sizes and one a referral (teaching) hospital, in Valencia, Spain. These were: 1) Hospital Universitari La Fe, a 900-bed teaching hospital serving a population of 400,000 and with 13 physicians specialising in lung diseases; 2) Hospital de Sagunto, a 270 bed community hospital serving a population 128,000 and with three lung specialists; 3) Hospital de Gandía, a 240-bed community hospital serving a population of 125,000 and with three lung specialists; and 4) Hospital de Requena, a 106-bed hospital serving a population of 58,000 and with two lung specialists. Patients consecutively admitted to the four hospitals during a 12-month period were included. Inclusion criteria were the presence of a chest radiograph with evidence of infiltrate and symptoms compatible with CAP. Alternative diagnoses were excluded during the follow-up period. Patients with immunosuppression, including human immunodeficiency virus infection, patients who had been hospitalised in the previous 15 days and those with tuberculosis were also excluded, as were those patients who received attention in the intensive care unit.

Data collection

A protocol was devised that sought data on demographical characteristics, comorbidity, initial evaluation of the risk class according to Fine, or the PSI [15], LOS and outcome. Data were collected as follows. In the first 24 h, the 20 variables that comprise the prognostic scale of Fine [15] were evaluated and the patient was classified in one of the five risk classes (range, I–V). Demographical characteristics including age, gender, smoking habit and alcohol intake were recorded. Specific comorbidity details included chronic obstructive pulmonary disease (COPD), asthma, cardiac diseases, renal or hepatic diseases, diabetes mellitus, prior hospitalisation or prior CAP. Concomitant medications, such as oral or inhaled corticosteroids and previous antimicrobial treatments, were also recorded.

Initial clinical symptoms and physical signs noted were pleural pain, cough, expectoration, abrupt onset dyspnoea, and the time-lapse (in days) from symptom onset. The presence of cyanosis, blood pressure measurement, respiratory rate, level of consciousness and auscultation data were also noted. Laboratory analyses recorded leukocyte, haematocrit, plasma urea (BUN), albumin, sodium, potassium and platelet levels and blood gas measurements (arterial oxygen tension (Pa,O_2), arterial carbon dioxide tension, and pH) on admission. Radiograph data on admission assessed the number of lobes affected and the presence/absence of pleural effusion.

Initial antimicrobial regimens prescribed were as follows: third generation cephalosporins, third generation cephalosporins and macrolides, macrolides alone, quinolones, amoxycillin-clavulanate alone or with macrolides, and other regimens. Antimicrobial treatment was classified as adhering, or not, to Spanish guidelines [18]. Adherence-to-guidelines treatment was defined as initial antimicrobial regimen consisting of third generation cephalosporins alone or with macrolides, amoxycillin-clavulanate alone or with macrolides and quinolones (third or fourth generation) alone. Other treatment regimens were defined as not adhering to the guidelines. LOS was defined as the number of days between admission and discharge.

Statistical analysis

Univariate analyses were performed using all the variables recorded on admission, the demographical characteristics, initial risk class, laboratory and radiograph data, and the number of days of hospitalisation. Pearson correlation analysis was used for data that followed a normal distribution and Spearman correlation for those that followed a non-normal distribution. All p-values of <0.05 were considered statistically significant.

The variables that were found to be significant ($p<0.05$) in the univariate analysis were introduced as independent variables in a multivariate stepwise linear regression analysis with the LOS (in days) as the dependent variable.

Results

Study population

A total of 425 patients admitted with CAP were included in the study. The demographical characteristics, comorbidity, PSI index and mortality in the four hospitals are summarised in table 1 and table 2. No differences were found between the four hospitals with respect to age, gender and previous comorbidities of the most frequent coexisting conditions, such as congestive heart failure, COPD, diabetes, renal disease and cerebrovascular disease. Active smokers were more frequent in Hospitals C and D ($p<0.02$). Mortality expressed as a function of each initial risk class showed statistically non-significant differences in the four hospitals (table 2).

The percentage distributions of patients in the teaching hospital with respect to PSI were 9.6, 10.9, 24, 39.3 and 16.2 in the risk classes I, II, III, IV and V, respectively. The differences in the distributions were not statistically different ($p=0.18$) from the corresponding percentage distributions in

Table 1. – Demographical characteristics, comorbidity and initial risk class of the patient cohort

Characteristic	Hospital A	Hospital B	Hospital C	Hospital D
Patients n	229	73	58	65
Age yrs[#]	69±16	70±16	68±17	72±16
Sex M/F	65/35	63/37	59/41	71/29
Residence for the elderly %	3.5	2.7	8.6	4.6
Alcohol %	16	7	19	21
Smokers %*	14.8	19.2	24	25
COPD %	32	41	31	34
Cardiac disease %	33	18	26	23
Diabetes %	22	18	22	14
Liver disease %	5	4	7	8
CNS disease %	15	11	15	19
Renal disease %	5	3	9	6

M: male; F: female; COPD: chronic obstructive pulmonary disease; CNS: central nervous system. [#]: data are presented as mean±SD. *: $p<0.05$.

Table 2. – Initial risk class and mortality

Risk class	Hospital A		Hospital B		Hospital C		Hospital D	
	% total	% dead	% total	% dead	% total	% dead	% total	% dead
PSI I	9.6	0	5.5	0	8.6	0	1.5	0
PSI II	10.9	0	12.3	0	13.8	0	15.4	0
PSI III[#]	24	5.5	23.3	0	27.6	0	7.7	0
PSI IV[#]	39.3	8.8	45.2	9.1	31	5.6	43.1	7.1
PSI V[#]	16.2	21.6	13.7	30	19	27.3	32.3	14.3
Total		8.7		8.2		6.9		7.7

PSI: pneumonia severity index. [#]: p=not significant.

the general hospitals (5.1, 13.8, 19.4, 40.3 and 21.4 in the risk classes I, II, III, IV and V, respectively).

Antibiotic therapy included the administration of third generation cephalosporins in 32 patients, amoxycillin-clavulanate in 39, quinolones in eight, macrolides in 32 and a combination of β-lactams and macrolides in 238. Other antimicrobial agents had been employed in 76 patients. Adherence to the Spanish guidelines, Sociedad Espanola de Neumología y Cirugía Torácica (SEPAR), with respect to empirical treatment was 75%. Significant differences were observed in the antimicrobial regimens prescribed in the four hospitals: in Hospital B, the adherence to the SEPAR guidelines was significantly lower.

Natural history of the illness and its outcome

There was an overall mortality rate of 8.2% (35 patients). There were no significant differences in the distribution of patients according to risk class for mortality and hospital (table 2). Logistic regression analysis was performed to predict death (dependent variable) using the initial risk class (according to Fine; classes I–V) and the type of hospital as independent variables. The model selected only initial risk class as a significant predictor of mortality (odds ratio 2.6).

Length of stay in hospital

Univarite analysis. The statistical analysis of duration of hospitalisation was performed and excluded those patients who died during hospitalisation. The median LOS in the group of patients who had died was 7 days (range, 1–27 days). The LOS segregated with respect to risk class is presented in table 3. LOS was shorter in Hospital D, $p<0.05$. Due to the skewed distribution of LOS, nonparametric tests were used.

The LOS in surviving patients, following the initial antibiotic treatment, was lower in those treated with quinolones and amoxycillin-clavulate+macrolides (p=0.035) (table 4). When the data were analysed with respect to adherence to SEPAR guidelines, there were no significant differences.

Spearman correlation analysis was performed using all the initial variables. Age, gender, alcohol intake, smoking habit and comorbidity were not significantly correlated with LOS. Significant positive correlations were observed with the PSI index, presence of pleural effusion, number of lobes affected and BUN concentration. Significant inverse correlations were observed with the P_aO_2 level on admission, concentration of albumin, presence of neoplasia and diastolic blood pressure.

Multivariate analysis. Three multivariate linear regression analyses were performed to predict the duration of hospitalisation (dependent variable). The first run included the total cohort, the second included only those patients in risk classes III, IV and V and the third included those patients in risk classes I and II. The independent variables were those found to be significant in the univariate analyses. Additional variables were initial antibiotic treatment, adherence to SEPAR guidelines, and the hospital to which the patients had been admitted (A, B, C and D: introduced into the analyses as dummy variables). The quantitative variables included were albumin concentration, diastolic blood pressure and arterial P_aO_2.

The mathematical model identified six independent variables for the whole cohort and for risk classes III–V. These were albumin, pleural effusion, P_aO_2 on admission, type of hospital (shorter stays in Hospitals C and D), number of lobes affected in the initial radiograph and diastolic blood pressure. The coefficients of the models and the estimation errors are presented in table 5. The mathematical model, when only the risk classes I–II were analysed, identified hypoxemia, pleural effusion and admission to Hospital D as being the only variables significantly related to LOS.

Table 3. – Initial risk class and duration of hospitalisation at each hospital

Risk class	Hospital A	Hospital B	Hospital C	Hospital D
PSI I	6 (7±4)	8 (8±3)	10 (9±2)	3 (3±0)
PSI II	8 (8±3)	8 (8±2)	9 (9±4)	4 (5±2)
PSI III	9 (11±6)	8 (9±5)	7 (8±2)	14 (14±7)
PSI IV	9 (10±6)	10 (11±5)	7 (9±4)	6 (7±5)
PSI V	9 (11±7)	8 (9±4)	11 (10±3)	7 (7±3)
Total	8 (10±6)	8 (10±4)	8 (9±3)	6 (7±5)

Data are presented as median (mean±SD). $p<0.05$.

Discussion

In the present study, different clinical variables were identified as being associated with LOS when the patient population was analysed on the basis of the initial risk class.

Table 4. – Duration of hospitalisation in relation to initial antibiotic treatment

Antibiotic regimen	Days of stay
Third generation Cephalosporin	8 (10±6)
Third generation Cephalasporin and macrolide	8 (10±5)
Amoxycillin-clavulanic acid	9 (10±7)
Amoxycillin-clavulanic acid and macrolide	6 (7±3)
Macrolide	8 (8±3)
Quinolone	6 (7±4)
Others	8 (9±4)

Data are presented as median (mean±SD). p=0.03.

Table 5. – Predictive factors of length of duration of hospitalisation

Variable in the model	Coefficient		
	Fine I–II[#]	Fine III, IV and V[¶]	Fine I–V[+]
Constant	8.8	18.3	18.4
Albumin mg·dL^{-1}		-1.5	-1.4
Pleural effusion	2.5	3.2	3.2
Pa,O_2 mm·Hg[§]	-0.058	-0.075	-0.08
Hospital D	-3.9	-3.07	-3.2
Number of lobes involved		1.59	1.4
Diastolic blood pressure		-0.059	-0.06
Hospital C		-0.07	-2.3

Pa,O_2: arterial oxygen tension. [#]: correlation coefficient (r)=0.55; SE=2.5, f value=8.7; [¶]: r=0.442, SE=4.9, f value=8.3; [+]: r=0.471, SE=4.6; f value=12.4; [§]: mm·Hg×0.133=kPa.

In the low-risk sub-groups I and II (as defined by Fine), hypoxemia and pleural effusion were the significant independent variables observed in the multivariate analysis. In risk classes III, IV and V, further variables were identified. These were diastolic blood pressure, multi-lobe involvement and albumin concentration. When adjusted for these variables, the type-of-hospital variable remained significantly different.

The current investigation was a multi-centre study designed to evaluate the clinical variables, at the first 24 h of admission to hospital, of a cohort of patients with CAP in four hospitals having different healthcare remits, and to determine the impact on LOS. Although there were no differences with respect to the characteristics of the patients when evaluated on comorbidity, demographical data and class of initial risk (except a higher numbers of smokers in Hospitals C and D) there were significant differences in the duration of hospitalisation. The mortality rate in each hospital evaluated for each initial risk class (as defined by Fine) did not show significant differences.

The authors encountered several factors that correlated (positively or negatively) with the LOS and which corresponded to the initial severity of the illness (PSI, or risk class of Fine), characteristics of the patients, initial antibiotic treatment and the type of hospital. Previous studies [9, 15, 16, 19] had observed (as did the current study) a correlation between greater initial severity of the illness and longer hospitalisation. However, prolonged hospitalisation in low-risk patients was also detected. The Fine scale had been designed and validated, originally, to predict mortality but has since been recommended for decisions regarding hospitalisation. For example, it is proposed that patients in low-risk classes I and II should be treated on an outpatient basis because of the low mortality risk. However, scientific guidelines are not necessarily a substitute for clinical judgement and when this prognostic scale is employed to decide whether to admit a patient, the percentage of admissions is reduced, but not eliminated [20, 21]. This may be due to the limitations associated with specific circumstances of the patients and the underestimation of risk in the younger-aged patients.

Less controversial is the need for admission for the higher risk classes III–V. Therefore, the authors decided to analyse the high-risk sub-group separately and compare the results with the low-risk group, since there is a greater consensus with respect to the decision to admit these high-risk patients.

The advantage of employing multivariate analysis is that it facilitates the selection of independent variables, while discarding those that contain redundant information or confounding variables. The current study also offers the opportunity to assess the influence of hospital type on LOS, since the patient types are similar with respect to clinical circumstances, as well as risk class.

In the mathematical model of the current study the authors encountered five independent variables that best predicted LOS for pneumonia in the overall patient cohort and in the high-risk classes III–V. The independent variables detected were initial hypoxemia, pleural effusion, levels of albumin, number of lobes affected in the initial radiograph and the initial diastolic pressure. The values of Pa,O_2, albumin and diastolic pressure were inversely related to LOS, while the converse applied to pleural effusion and the number of lobes affected in the initial radiographs. However, in the low-risk classes only two of these clinical factors were detected: hypoxemia and pleural effusion.

Respiratory insufficiency is a morbidity and mortality risk factor that occurs with CAP and is one of the main reasons for hospital admission [22, 23]. HALM *et al.* [24] observed that the resolution of hypoxemia was the clinical parameter that required more days of hospitalisation to achieve clinical stability. Similarly, the presence of pleural effusion with CAP predisposes a protracted hospitalisation, since this condition requires greater clinical attention, radiological follow-up, thoracocentesis and, eventually, drainage of the thorax. In the current study the authors noted that this was one of the principal motives for hospitalisation and prolonged duration of hospital stay, in risk-class I in Hospital C. ROSON *et al.* [25], in a prospective observational study evaluating hospitalisation on the basis of conventional criteria *versus* PSI, indicated that 60% of patients classified as low risk class (I and II of Fine) needed supplemental oxygen or had pleural complications and these were the reasons for which they were hospitalised.

Hypoxemia and pleural effusion are the two clinical factors that can be underestimated in the prognostic scale of Fine, especially in young patients, and account for the admission rates in the risk-classes I and II. In a very recent editorial, HALM and TEIRSTEIN [26] state that all patients with hypoxemia (Pa,O_2<7.98 kPa (60 mm·Hg) while breathing room air) or metastasic disease or empyema should be hospitalised regardless of the score on the Fine scale.

In risk-classes III–V, the effects of hypoxemia and pleural effusion on LOS are associated with three additional clinical variables. Malnutrition is clearly associated with the gravity of the pneumonia and its poorer prognosis [27]. Further, it is more frequent in the elderly and contributes to a slower clinical response to treatment [27, 28]. Several studies have shown that albumin is a marker of nutritional status and is associated with mortality risk and recovery time of the patient. Multi-lobe involvement and low diastolic blood pressure are risk factors for a complicated clinical course of disease and, as such, it is not surprising that these variables were related to a longer LOS.

The influence of the clinical variables on LOS found in the current study is not unexpected, since they are related to the clinical instability and initial gravity. However, the authors were unable to evaluate the correlations with the time required to reach clinical stability or with the therapeutic response. From this perspective, the association between the initial clinical variables and the resolution of the infection parameters would have provided more insight into clinical and nonclinical factors related to LOS.

With respect to the initial antibiotic regimen employed, univariate analysis indicated that there was a shorter LOS in those patients treated with amoxycillin–clavulanate and macrolides or quinolones. However, this variable was not subsequently selected in the multivariate model. Previous studies that analysed the influence of treatment on the duration of hospitalisation obtained discordant results [29, 30]. Adherence, or not, to the SEPAR guidelines for the

treatment of CAP did not relate significantly with LOS, as has been reported previously by the authors [31] and others [32].

The type of hospital to which the patient was admitted was a factor predictive of LOS. McCormick *et al.* [9] had reported that, for a similar risk class, there were differences in hospitals with respect to the duration of stay but without negative effects on several outcomes, such as mortality and re-admission. However, the results reported in the literature are not completely concordant, since some authors highlight possible negative consequences for patients after a shortened stay in hospital [12, 33].

The variability in the duration of hospitalisation with respect to hospital type emphasises the need for objective criteria for the treatment of CAP, so as to reduce the differences in the clinical management of this condition [13, 17, 34, 35]. These aspects are beginning to be incorporated in the latest guidelines of the American Thoracic Society [23].

As a limitation of the study, the authors wish to highlight that the mathematical model obtained is not ideal, since the amount of variance explained by the model is not high. However, other variables exist which are not strictly clinical and/or quantifiable and which can influence the LOS. These include hospital inefficiencies, clinical professionals′ preferences/idiosyncrasies and difficulties in the management of the patient on an outpatient basis. Another limitation is that the authors did not evaluate the relationships between initial variables and clinical stability and/or clinical response-to-therapy separate from the LOS so as to distinguish the impact of other factors, such as social variables, on LOS. Nevertheless, the authors consider that the information gathered is valuable for the clinician and healthcare workers, since it provides a rule of thumb to indicate the probable requirements with respect to length of hospitalisation in CAP.

In summary, in the present study of community-acquired pneumonia the authors observed that in low-risk patients, the length of stay is determined mainly by the level of hypoxemia and pleural effusion, while in the higher risk classes, additional factors, such as multi-lobe involvement, diastolic blood pressure and the albumin concentration, also become significant. The hospital where the patient was admitted exerts an effect on length of stay that is independent of the clinical variables and the severity of the patient′s illness on admission. A further area of investigation would be to quantify the influence of variables, such as clinical stability and response to therapy, and length of stay.

Acknowledgement. Editorial assistance was by P.R. Turner of t-SciMed, Reus, Spain.

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