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Antibioticoterapia empírica en la neumonía comunitaria grave: impacto sobre la mortalidad tras la administración de dos antibióticos de forma precoz

Tesis presentada por

SIMONE GATTARELLO

Para optar al grado de Doctor

Directores: **Jordi Rello Condomines y Vicenç Falcó Ferrer**

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Jordi Rello Condomines, Profesor Titular de la Facultad de Medicina de la Universidad Autónoma de Barcelona y Jefe de Servicio del Servicio de Medicina Intensiva del Hospital Universitario Vall d'Hebron

y

Vicenç Falcó Ferrer, Profesor Titular de la Facultad de Medicina de la Universidad Autónoma de Barcelona y Médico Adjunto del Servicio de Enfermedades Infecciosas del Hospital Universitario Vall d'Hebron

Certifican que la tesis titulada:

"Antibioticoterapia empírica en la neumonía comunitaria grave: impacto sobre la mortalidad tras la administración de dos antibióticos de forma precoz"

Que presenta el licenciado **Simone Gattarello**, ha sido realizada bajo su dirección en el Servicio de Medicina Intensiva del Hospital Universitario Vall d'Hebron, la consideran finalizada y autorizan su presentación para que sea defendida ante el tribunal que corresponda.

Dr. Jordi Rello Condomines **Dr. Vicenç Falcó Ferrer**

En Barcelona, 14 de Octubre de 2015

A mis padres y mi familia

A todos mis amigos

A todos los compañeros de este grandísimo viaje

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Gattarello S, Lagunes L, Vidaur L, Solé-Violan J, Zaragoza R, Vallés J, Torres A, Sierra R, Sebastian R, Rello J. "Improvement of Antibiotic Therapy and ICU Survival in Severe Non-Pneumococcal Community-Acquired Pneumonia: a Matched Case-Control Study". Critical Care. 2015; 19: 335. (Impact Factor 2014: 4.48)

Otros artículos originales (Anexo):

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Gattarello S, Ramírez S, Almarales JR, Borgatta B, Lagunes L, Encina B, Rello J. "Causes of non-adherence to therapeutic guidelines in severe community-acquired pneumonia". Revista Brasileira de Terapia Intensiva. 2015; 27: 44-50.

Artículos de revisión (Anexo):

Gattarello S. “What is new in antibiotic therapy in community-acquired pneumonia? An evidence-based approach focusing on combined therapy”. Current Infection Disease Reports. 2015; 17: 501.

ÍNDICE

ABREVIATURAS

NAC: Neumonía Adquirida en la Comunidad.

EPOC: Enfermedad Pulmonar Obstructiva Crónica.

RCP: Reanimación Cardiopulmonar.

UCI: Unidad de Cuidados Invasivos.

NACG: Neumonía Adquirida en la Comunidad Grave.

ERS/ESCMID: Sociedad Respiratoria Europea/Sociedad Europea de Microbiología Clínica y Enfermedades Infecciosas (European Respiratory Society-European Society for Clinical Microbiology and Infectious Diseases).

IDSA/ATS: Sociedad Norteamericana de Enfermedades Infecciosas-Sociedad Torácica Norteamericana (Infectious Diseases Society of America/American Thoracic Society).

CURB 65: Confusion, Uraemia, Respiratory Rate, Blood Pressure.

PSI: Pneumonia Severity Index.

VMI: Ventilación mecánica invasiva.

I. INTRODUCCIÓN

INTRODUCCIÓN

La neumonía comunitaria: historia y evolución de la mortalidad

La infección pulmonar ha sido una enfermedad de elevada prevalencia durante toda la historia del hombre. Los síntomas fueron inicialmente catalogados en el siglo IV a.C. por Hipócrates de Cos (1), que se refiere a la neumonía como: "la enfermedad nombrada por los ancianos". Posteriormente, Moses Maimonides, médico y filósofo de la edad media, describió en el siglo XII los signos y síntomas de la neumonía tal y como hoy en día se definen: fiebre alta, dolor pleural, taquipnea y tos (2).

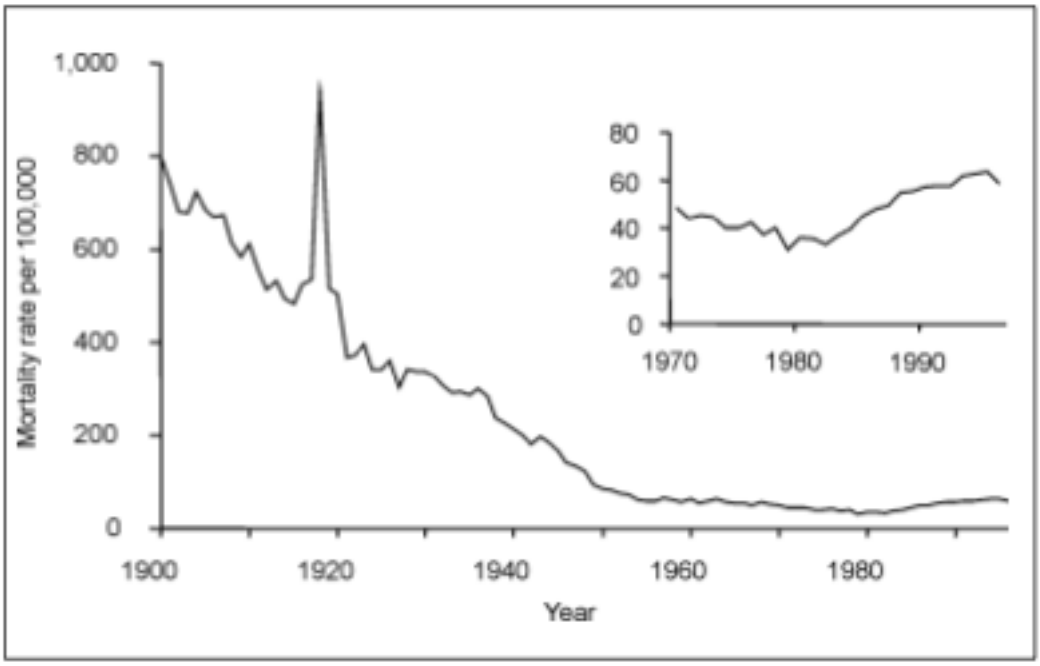
En 1875, el Dr. Edwin Klebs fue el primero en aislar y documentar la presencia de bacterias en la vía aérea de individuos fallecidos por neumonía (3). Así pues, entre 1882 y 1884 se realizaron los estudios que permitieron identificar los más frecuentes microorganismos causantes de neumonía: *Streptococcus pneumoniae* y *Klebsiella pneumoniae* (4-6).

El Dr. William Osler, considerado el padre de la medicina moderna, destacó la peligrosidad y virulencia de la neumonía mediante la siguiente definición: "el capitán de los hombres de la muerte" (7). Esta definición fue realizada en torno al año 1918 que, según los registros demográficos, es cuando la neumonía adelantó la tuberculosis como primera causa de fallecimiento en el mundo desarrollado (8). En aquel entonces, la neumonía era una enfermedad sin posibilidades médicas de curación, con una tasa de mortalidad muy elevada, que algunos autores estiman en un 30% en los casos hospitalizados (9); pese al avance de los conocimientos microbiológicos alcanzados en las décadas anteriores, pocos cambios se observaron en cuanto a mortalidad (9).

Por otro lado, debido al desarrollo en el campo de la medicina que se verificó durante el siglo XX, básicamente el descubrimiento de la

penicilina inicialmente y luego de otros antibióticos (10), la mortalidad secundaria a neumonía adquirida en la comunidad (NAC) presentó una drástica reducción (figura 1).

Figura 1: evolución de la mortalidad por neumonía en el siglo XX.



Paralelamente, el desarrollo de unas técnicas quirúrgicas más efectivas y el comienzo de la historia de los cuidados intensivos permitió incrementar la reducción de la mortalidad (11,12). Además, la disponibilidad en las décadas posteriores de las nuevas vacunas frente a *Haemophilus influenzae* y *Streptococcus pneumoniae*, las primeras disponibles para patógenos respiratorios, condujo a una disminución de la incidencia de la neumonía, y como consecuencia una disminución de la tasa absoluta de mortalidad de la neumonía (13,14).

Finalmente, en las últimas décadas, la cada vez mejor atención médica proporcionada a los paciente con neumonía, permitió reducir ulteriormente su mortalidad (12). Sin embargo, pese a la escasez de datos en este contexto, algunos autores afirman que desde los años ochenta hasta hoy en día, la tasa de mortalidad por neumonía habría vuelto nuevamente a aumentar (15). Esta observación se justificaría a raíz de un aumento de enfermos crónicos y con menos reserva funcional, en los que la neumonía condicionaría una evolución clínica desfavorable (12). De hecho, se ha descrito como en pacientes con historia de inmunodepresión, cardiopatía y enfermedad pulmonar obstructiva crónica (EPOC), la tasa de mortalidad es mayor con respecto al resto de la población (16). Otros estudios concluyen que debido a los avances en el cuidado de los pacientes más graves, la mortalidad de estos pacientes, incluyendo aquellos con neumonía, habría disminuido (17,18).

De todos modos, como previamente se ha mencionado, el avance más crucial para una disminución significativa de la mortalidad en la neumonía comunitaria, ha sido el descubrimiento de la penicilina, por Alexander Fleming, en 1928 (19).

Aunque en la literatura se han reportado datos a favor de una tendencia a mayor mortalidad en las últimas décadas, estos datos deberían de ser interpretados con cautela. Esto se debe a que los datos demográficos de que originan estos estudios muy a menudo no diferencian entre los casos de neumonía en pacientes previamente sanos de los episodios que afectan individuos con enfermedades graves y orden de no realización de reanimación cardiopulmonar (RCP).

No obstante todos los avances realizados, hoy en día la neumonía comunitaria sigue constituyendo un problema sanitario muy relevante,

ya que en sus formas más graves se asocia a elevada morbilidad y mortalidad (20). La incidencia global de neumonía comunitaria se estima en unos 450 millones de individuos cada año (21) de los cuales unos 4 millones fallecerán (19,22), siendo así la primera causa de muerte por infección en el mundo desarrollado (23,24). Además, los costes de tratamiento de la neumonía son muy elevados, se estimó en Estados Unidos en el año 2012 un coste global para el tratamiento de la neumonía de unos 20 billones de dólares (25), el coste promedio para el tratamiento de un caso de neumonía que requiere admisión hospitalaria, en 2012, fue algo más de 15 mil dólares por individuo (26).

En la práctica clínica diaria, la manera más inmediata para clasificar las diferentes gravedades de neumonía, es categorizar entre formas leves, moderadas y graves. Según datos recientes, la mortalidad estimada en las diferentes formas de neumonía es la siguiente: alrededor del 1% en los casos leves, en torno a un 10/12% en las formas moderadas y entre un 20 y 50% en las neumonías graves (27).

En el caso de la neumonía grave, la variabilidad en la tasa de mortalidad se justifica principalmente por los diferentes criterios de ingreso en la Unidas de Cuidados Intensivos (UCI) en los diferentes centros, que depende esencialmente de la disponibilidad y organización de las camas de críticos en cada institución (19,28).

Neumonía comunitaria grave: definición y epidemiología

A pesar de la importancia que tiene determinar la gravedad del paciente con neumonía, no existe hasta ahora una definición exacta y universalmente aceptada de neumonía adquirida en la comunidad grave (NACG) (29). En la mayoría de los estudios se ha usado una definición

operacional, se considera NACG aquella neumonía que requiere ingreso en UCI (30). Sin embargo, los criterios empleados para admitir a estos pacientes en la UCI aún no han sido claramente definidos, y pueden variar dependiendo de la experiencia del médico responsable y las normativas del hospital (31).

Leeper et al. propusieron una definición operacional simple para NACG, que sería cuando el paciente necesita de la vigilancia y monitorización de una UCI y que permita, si es necesario, apoyo con conexión a un ventilador mecánico o soporte hemodinámico (32). Posteriormente, en un intento por lograr una mejor definición de neumonía comunitaria grave, se han desarrollado varios sistemas de puntuación y modelos predictores para ayudar al médico clínico a identificar precozmente a estos pacientes (33,34). Sin embargo, ninguno de ellos como veremos a continuación, ha logrado una segura categorización del riesgo particular de cada paciente (35).

Para mejor clasificar las diferentes formas de neumonía, y para un mejor cuidado de los pacientes con neumonía, varias sociedades científicas publicaron recomendaciones para el manejo de la neumonía adquirida en la comunidad (36-38), incluyendo la Sociedad Respiratoria Europea y la Sociedad Europea de Microbiología Clínica y Enfermedades Infecciosas (ERS/ESCMID) (39). En estas recomendaciones se indican criterios para la clasificación de gravedad de neumonía, su definición y recomendaciones sobre el sitio más indicado para el tratamiento del paciente.

Sin embargo, en la práctica clínica diaria la neumonía comunitaria grave se continua definiendo como aquella neumonía que requiere ingresar el paciente en UCI, debido a la presencia de insuficiencia respiratoria severa, shock séptico, o alguna otra insuficiencia de órgano grave que

requiere monitorización invasiva (36). De la misma manera, se considera neumonía leve aquella neumonía adquirida en la comunidad que se decide tratar de forma ambulatoria, y neumonía de gravedad moderada aquella que condiciona ingreso en la planta de hospitalización (36).

En cuanto a la prevalencia de las varias formas de neumonía, es muy difícil estimar la porcentual de neumonías leves y moderadas, o sea de aquellas neumonías que se tratan de forma ambulatoria o en planta de hospitalización. De hecho, se ha observado en la literatura una elevada variabilidad a la hora de tratar una neumonía leve-moderada en régimen ambulatorio o de hospitalización (40). Se ha descrito además como una significativa mayoría de los médicos tiene la tendencia de sobreestimar la gravedad de los pacientes con neumonía leve, ingresando un número de pacientes mayor de lo realmente necesario (41,42). Por otro lado, las neumonías comunitarias que requieren tratamiento en la UCI representan entre el 10 y 30% de los pacientes hospitalizados por NAC (43), directamente desde su llegada a urgencias o de forma tardía desde la planta por mala evolución clínica (44,45).

A destacar, un problema generalizado de la mayoría de artículos realizados sobre neumonía comunitaria es que no hay diferenciación entre formas leves, moderadas y graves; esto tiene implicaciones importantes, debido a la diferente mortalidad según la severidad (46). Además, en muchas ocasiones los criterios de clasificación de la gravedad de la neumonía son diferentes según el centro que realizó el estudio, ya que cada institución tiene recursos diferentes en forma de disponibilidad de camas con posibilidad de monitorización semi-intensiva, intermedia o mínima, además de diferencias en la organización de las plantas o de las UCIs (47).

Escalas pronósticas en la neumonía comunitaria

Debido a las implicaciones personales y económicas en el paciente diagnosticado de neumonía, la estimación de la severidad de la neumonía es un momento de fundamental importancia en el manejo de la NAC y debería de realizarse de forma muy cautelosa (48). Tras el diagnóstico de neumonía, la decisión del sitio óptimo para el manejo del paciente es probablemente la decisión más complicada (49). El gasto de manejo de un paciente hospitalizado puede ser hasta 25 veces mayor que el gasto de un paciente ambulatorio (50). Además, pacientes con neumonía leve tratados de forma ambulatoria recuperarán una funcionalidad normal precozmente con respecto a individuos hospitalizados (51,52). Por otra parte el riesgo de trombo-embolismo pulmonar e infección nosocomial aumentan en un régimen de hospitalización (53). Finalmente, los microorganismos que condicionan neumonía moderada a grave no son los mismos que originan neumonía leve (54,55), lo que implica regímenes de tratamiento antibióticos diferentes en las diferentes formas de neumonía (56,57).

Para intentar establecer el nivel de gravedad de una neumonía, varios factores tienen que ser tenidos en cuenta; la etiología, la situación clínica, radiológica y analítica y la posibilidad de beneficio para el paciente del uso de tratamientos específicos son los aspectos más relevantes.

En la práctica clínica diaria, debido a su sencillez e inmediatez, la clasificación más empleada para identificar las formas graves de neumonía, es la escala propuesta en las recomendaciones por las Sociedad Norteamericana de Enfermedades Infecciosas/Sociedad Torácica Norteamericana (IDSA/ATS) (36). Según los criterios propuestos

en estas recomendaciones, se indica ingreso en UCI en caso de por lo menos un criterio mayor o tres criterios menores. Los criterios mayores y menores son indicados en la figura 1. La importancia de identificar los pacientes que requieren ingreso en UCI se justifica por una mayor optimización de los recursos médicos empleados (58). Además, el ingreso retrasado en UCI de pacientes con neumonía procedentes de planta de hospitalización se asocia a mayor mortalidad (59).

Figura 2: criterios para severidad según IDSA/ATS.

Criteria for severe community-acquired pneumonia.

Minor criteria
Respiratory rate ⩾30 breaths/min
PaO_2/FiO_2 ratio ⩽250
Multilobar infiltrates
Confusion/disorientation
Uremia (BUN level, ⩾20 mg/dL)
Leukopenia[c] (WBC count, <4000 cells/mm^3)
Thrombocytopenia (platelet count, <100,000 cells/mm^3)
Hypothermia (core temperature, <36°C)
Hypotension requiring aggressive fluid resuscitation
Major criteria
Invasive mechanical ventilation
Septic shock with the need for vasopressors

Varias otras escalas se propusieron para establecer la gravedad de una neumonía y predecir su mortalidad, aunque su uso no es rutinario en la mayoría de los centros y su utilidad se hace más evidente en la investigación clínica para estandarizar pacientes de centros diferentes. La escala de severidad Confusion, Uraemia, Respiratory Rate, Blood

Pressure (CURB-65), o la escala pronóstica Pneumonia Severity Index (PSI), pueden ayudar en la identificación de neumonía leve, moderada o grave (41,42).

La escala PSI es una puntuación predictiva basada en parámetros clínicos validada en más de 50 mil pacientes, ambulatorios y hospitalizados. La escala se publicó por primera vez en 1989, y estratifica los pacientes en 5 clases, cada una asociada a una mortalidad diferente a los 30 días. La escala fue diseñada originalmente para identificar a pacientes con neumonía que tienen bajo riesgo de muerte, por tanto, que pueden ser tratados de forma ambulatoria (33). Varios estudios han confirmado su habilidad de predicción de mortalidad en la neumonía (60), sin embargo en ocasiones se producen discrepancias significativas al comparar los criterios convencionales de ingreso en UCI y la puntuación PSI (61). Dependiendo de la mortalidad asociada a cada clase de gravedad, se recomienda tratar de forma ambulatoria pacientes con puntuación de I y II; los pacientes en clase III deberían de mantenerse bajo observación antes de decidir la ubicación de tratamiento, o mantenerse ingresados los primeros días de tratamiento; finalmente, los pacientes en clase IV o V deberían de ser hospitalizados (33). Los parámetros que se valoran en esta escala son: edad, confusión, frecuencias cardiaca y respiratoria, presión arterial, temperatura corporal, historia de enfermedad tumoral, cardiaca, renal y hepática.

La escala CURB 65 es una escala de predicción de mortalidad avalada por la British Thoracic Society que estima la severidad de la neumonía comunitaria tras valoración de unos 5 parámetros (34). Los parámetros evaluados son: presencia de confusión, uremia, frecuencia respiratoria, presión arterial y edad mayor de 65 años. Cada individuo es estratificado

en una escala de 0 a 5, aumentando el riesgo de fallecimiento a los 30 días al aumentar la clase de pertenencia CURB 65. La ventaja más relevante de esta escala es su sencillez y rapidez de cálculo; la presencia o ausencia de cada uno de los cinco parámetros a valorar suma o no un punto, alcanzando un valor total de entre 0 y 5. En caso de puntuación de 0 y 1 no se recomienda hospitalización y con puntuación de 2 o 3 se recomienda ingreso durante los primeros días de tratamiento; finalmente, una puntuación de 4 o 5 implica hospitalización. Si bien la capacidad de prever la mortalidad de las escalas PSI y CURB 65 es equiparable, el PSI demostró mejor sensibilidad, mientras que el cálculo del CURB 65 es más rápido y sencillo (62). Además, la puntuación PSI es más sensible para identificar pacientes con bajo riesgo de mortalidad con respecto al CURB 65 (63). Hoy en día no existe ningún ensayo clínico que haya comparado la capacidad de discriminación de gravedad de las dos escalas, con lo que no está claro si una escala es superior a la otra.

Debido a su sencillez de uso, el escore CURB 65 es usualmente preferido frente al PSI para identificar pacientes cuyo ingreso en UCI sería beneficioso. Además, el CURB 65 fue diseñado para estimar la gravedad de neumonía más que para prever la mortalidad; pacientes con puntuación superior a 2, además de un mayor riesgo de mortalidad, presentan en general una alteración fisiológica más importante que podría requerir una monitorización o un tratamiento más intensivos (34). Es importante destacar que estos criterios no se han validados en estudios prospectivos.

Recomendaciones internacionales y tratamiento de la neumonía comunitaria

Varias sociedades científicas nacionales e internacionales publicaron en las últimas décadas recomendaciones para el diagnóstico y tratamiento de la neumonía comunitaria. En concreto, las guías más citadas en la literatura internacional son la norteamericana, producida por las IDSA/ATS (36), la británica que es editada por la British Thoracic Society (37), y la europea, promulgada por las ERS/ESCMID (39). Además de la elevada morbimortalidad y costes de tratamiento que condiciona la neumonía, un cuidado no óptimo puede conducir a un número mayor de complicaciones, que se asocian a un ulterior aumento de la mortalidad (64); estos son las razones más importantes para justificar la existencia de tales recomendaciones. Como regla general, las diferentes recomendaciones no varían mucho en cuanto a indicaciones terapéuticas, eso es debido a que la evidencia disponible es la misma en todas las regiones del mundo. Las diferencias que se pueden observar dependen en mayor medida de los cambios sociales presentes en las diferentes regiones del mundo.

La adherencia a las recomendaciones se ha asociado en varios estudios a una mayor supervivencia (65,66), sin embargo estas no tienen en cuenta las diferencias entre los diferentes pacientes, por esta razón, deberían de ayudar el clínico a decidir una actitud terapéutica, y no sustituirse al clínico. Además, todas las recomendaciones destacan unívocamente la importancia de la realización de indicaciones locales, para adecuar las recomendaciones a la población local, a los microorganismos más frecuentes en un determinado entorno, y finalmente para que las

indicaciones propuestas por la guía sean compatibles con los recursos presentes en un determinado entorno social (36,38,39).

Todas las guías abarcan aspectos diferentes en el manejo clínico del paciente con neumonía: el mejor sitio de tratamiento, el diagnóstico, las indicaciones sobre el tratamiento antibiótico empírico y dirigido y, finalmente, el tratamiento de los casos sin respuesta clínica o el tratamiento de complicaciones de la neumonía.

En el caso de las recomendaciones IDSA/ATS (36) el primer apartado abarca el proceso de decisión del sitio de manejo del paciente con neumonía. Como se ha observado previamente la clasificación admite las opciones de tratamiento domiciliario, en régimen de hospitalización o el ingreso en UCI. En este apartado, se discuten los riesgos y beneficios de tratar un paciente con neumonía en los varios ámbitos contemplados, utilizando toda la literatura pertinente disponible para poder establecer las recomendaciones; se describen las diferentes escalas pronósticas de gravedad, analizando los aspectos más fiables y menos exactos de cada escala. En el segundo apartado se indican las técnicas disponibles para el diagnóstico clínico de neumonía, el diagnóstico microbiológico y el diagnóstico de las posibles complicaciones médicas. Dependiendo de la evidencia científica disponible se recomienda la realización de un número específico de pruebas diagnósticas, que varía en función de las características del paciente, del microorganismo sospechado y de la gravedad de la neumonía, entre otros factores.

En otro apartado de especial importancia, se discuten las recomendaciones del tratamiento antibiótico. La primera parte de este apartado es dedicada al tratamiento antibiótico empírico, que es específico según la gravedad de la neumonía, además de depender de

otras características específicas de cada paciente. En un segundo apartado, se recogen las indicaciones sobre el tratamiento dirigido; en esta sección se discuten las mejores opciones antibióticas dependiendo del tipo de microorganismo aislado, y la duración del tratamiento. Para la realización de este apartado, se hace evidente la necesidad de disponer de una elevada información sobre datos de resistencias microbianas, de los microorganismos más frecuentes causantes la neumonía, además de estudios de comparación entre diferentes pautas antibióticas. En el apartado sucesivo se discuten el tratamiento de las complicaciones de la neumonía, y el manejo de la neumonía refractaria al tratamiento. Finalmente, en la última sección se discuten las opciones disponibles para la prevención de la neumonía, básicamente las vacunas para neumococo y para influenza.

Tratamiento antibiótico empírico en la neumonía comunitaria

Pese a la evidencia científica producida en las últimas décadas para identificar las pautas antibióticas asociadas a menor mortalidad en las diferentes formas de neumonía comunitaria, quedan todavía muchos interrogantes y el debate sigue vivo. Además, gracias a la disponibilidad de nuevas moléculas antibióticas en los próximos años, debido a los probables cambios en las resistencias antibióticas de los principales microorganismos causa de neumonía, y a causa de los cada vez mayores conocimientos sobre la interacción molecular entre microorganismo, antibiótico y sistema inmune, el tratamiento propuesto actualmente para el tratamiento empírico de la neumonía está desinado a cambiar en los próximos años.

En la actualidad, pese a las dudas todavía presentes, los datos procedentes de las principales recomendaciones y de los últimos estudios científicos publicados sugieren la administración de las siguientes pautas antibióticas, en caso de neumonía comunitaria.

En caso de pacientes con neumonía leve y sin factores de riesgo para mala evolución clínica, los datos actualmente disponibles recomiendan la administración de monoterapia con una quinolona, un macrólido o un betalactámico (36). Si bien se desaconseja el uso de quinolonas como primera opción, por el riesgo de aparición de resistencias (67), no se observaron diferencias de mortalidad tras la administración de una familia de antibiótico u otra (68). Es interesante destacar como por un lado las recomendaciones norteamericanas recomiendan cobertura de agentes típicos y atípicos, mientras las recomendaciones europeas admiten la administración de una pauta no activa frente a agentes atípicos (36,39). Esta conclusión procede de la observación que la falta de cobertura de atípicos en caso de neumonía leve no se asocia a mayor mortalidad (69). En caso de pacientes con neumonía leve y presencia de factores de riesgo para mala evolución, debido al elevado riesgo de neumonía por enterobacterias o por microorganismos resistentes, hay consenso sobre la necesidad de cobertura de microorganismos típicos y atípicos (70,71); pese a no documentarse diferencias en mortalidad, la cobertura de típicos y atípicos se asoció en varios estudios a una disminución de los costes de tratamiento, debido a una inferior tasa de fracasos terapéuticos, que se asocia a una menor tasa de ingresos hospitalarios (72).

En caso de neumonía moderada que requiere hospitalización, si bien datos antiguos contraindicaban la administración de un betalactámico en

monoterapia (73-75), en un estudio mas reciente se observan desenlaces clínicos comparables tras la administración de monoterapia con betalactámico comparado con otras pautas (76). En general se recomienda la administración de monoterapia con una quinolona respiratoria o un betalactámico, o una asociación entre un betalactámico y un macrólido. La indicación de tratamiento combinado tiene todavía más consistencia científica en caso de neumonía moderada asociada a bacteriemia neumocócica, asociada a presencia de factores de riesgo para mala evolución clínica (77), en caso de sospecha de infección por microorganismos atípicos (78), con puntación PSI de IV o V (79).

En caso de neumonía grave y necesidad de ingreso en UCI hay evidencia suficientemente sólida para justificar en todos los casos la cobertura de agentes típicos y atípicos (80). Por un lado, algunos estudios concluyen que la monoterapia y el tratamiento combinado condicionen una mortalidad comparable (81,82), mientras que otros documentan inferioridad en cuanto a eficacia clínica, por parte de la monoterapia (83,84). Pese a que el asunto no esta todavía completamente aclarado, de momento la evidencia parece deponer a favor del tratamiento combinado. Además, parece que la administración de una asociación entre un betalactámico y un macrólido sería la opción asociada a la inferior mortalidad (85) debido al efecto antiinflamatorio propio de los macrólidos (86,87). A destacar que no hay significación estadística para confirmar esta observación, y los datos obtenidos muestran una tendencia estadística no significativa.

Causas de no adherencia a las recomendaciones internacionales en la neumonía grave

La antibioticoterapia es una de las herramientas más efectivas para disminuir la mortalidad (88). Se ha descrito ampliamente cómo la administración de un antibiótico inadecuado en el shock séptico de origen respiratorio se asocia a un significativo aumento de la morbimortalidad (89-91) y de las multirresistencias (92). Varios estudios realizados en Europa (93,94), Estados Unidos (95) y Australia (96) analizaron la tasa de adherencia a las guías terapéuticas en la prescripción antibiótica empírica en individuos con neumonía comunitaria. Como regla general, la mayoría de estos estudios, documenta una amplia variabilidad en cuanto a adherencia a la recomendaciones, con tasas de adherencia entre un 20 y un 100% (94). Las causas propuestas para justificar la falta de adherencia fue la diferencia entre el paciente a tratar y el la patología descrita en la recomendación, presencia de insuficiencia renal o hepática, los costes excesivos de algunos antibióticos y la diferencia entre la flora local y las recomendaciones internacionales (97).

II. JUSTIFICACIÓN DEL ESTUDIO E HIPÓTESIS DE TRABAJO

JUSTIFICACIÓN DEL ESTUDIO E HIPÓTESIS DE TRABAJO

Justificación del estudio

Los datos sobre la evolución en las últimas décadas de la mortalidad secundaria a neumonía comunitaria grave bacteriana son muy escasos. En el caso de la neumonía comunitaria grave no hay datos publicados, ya que la mayoría de los artículos actualmente disponibles no diferencian entre formas leves moderadas y severas de neumonía.

La antibioticoterapia empírica es uno de los pilares del manejo clínico de los pacientes con neumonía comunitaria grave bacteriana; según las recomendaciones internacionales sobre el manejo clínico de los pacientes con neumonía, todos los casos de neumonía comunitaria grave bacteriana grave deberían de recibir dos antibióticos de forma precoz. Se ha demostrado que un tratamiento antibiótico empírico no adecuado se asocia a mayor mortalidad.

Aunque la mayoría de los estudios realizados para profundizar los conocimientos sobre antibioticoterapia empírica en la neumonía grave concluye que la administración de dos antibióticos de forma precoz se asocia a inferior mortalidad, algunos estudios no obtuvieron los mismos resultados. Además, gracias a la disponibilidad de nuevas familias antibióticas la observación de mayor supervivencia tras tratamiento combinado se ha cuestionado. Por ello, todavía no hay consenso sobre el tratamiento antibiótico empírico óptimo a administrar en pacientes con neumonía comunitaria grave.

Debido a la elevada mortalidad que condiciona la neumonía comunitaria grave bacteriana, debido a la importancia de individuar aquellas actuaciones médicas que podrían asociarse a una mayor supervivencia y debido al alto riesgo de la emergencia de nuevas resistencias bacterianas

tras una inadecuada política antibiótica, el estudio del tratamiento antibiótico empírico óptimo es de importancia fundamental, y justifica el interés de desarrollar el presente estudio.

Hipótesis de trabajo

En las últimas décadas la tasa de mortalidad por neumonía comunitaria grave bacteriana ha disminuido, y un mayor uso de tratamiento antibiótico combinado y la administración precoz del tratamiento antimicrobiano podrían ser responsables de esta tendencia.

III. OBJETIVOS

OBJETIVOS

El objetivo general del presente estudio es explorar eventuales cambios en la mortalidad por neumonía comunitaria grave bacteriana en las últimas décadas, e investigar si la administración precoz de dos antibióticos de forma empírica se asocia a cambios en la mortalidad. Este objetivo genérico se ha dividido en tres objetivos más específicos.

Objetivo principal

Explorar si en las últimas décadas hubo cambios en la tasa de mortalidad por neumonía grave bacteriana adquirida en la comunidad.

Objetivo secundario

Estudiar si la administración de dos antibióticos de forma empírica se asocia a una disminución de la mortalidad en pacientes con neumonía comunitaria grave bacteriana.

Objetivo terciario

Estudiar si la administración precoz de la antibioticoterapia empírica se asocia a una disminución de la mortalidad en pacientes con neumonía comunitaria grave bacteriana.

IV. METODOS

METODOS

Población a estudio

Para la realización del presente estudio caso-control se seleccionaron pacientes reclutados en los estudios prospectivos y multicéntricos CAPUCI I y CAPUCI II.

Los estudios CAPUCI I y CAPUCI II

El estudio CAPUCI I es un estudio multicéntrico prospectivo observacional realizado en 33 UCIs españolas desde 2000 hasta 2002. El estudio CAPUCI II es un estudio de seguimiento del CAPUCI I, avalado por la Sociedad Europea de Cuidados Intensivos, realizado en 29 UCIs europeas desde 2008 hasta la actualidad. De forma parecida en los dos estudios, todos los pacientes admitidos en la UCI por neumonía comunitaria grave fueron incluidos en el estudio. Se realizó seguimiento hasta el fallecimiento o hasta el alta de la UCI. Todas las decisiones clínicas y de manejo instrumental y farmacológico del paciente no eran protocolizadas y se realizaron a discreción del médico responsable del paciente.

Período de estudio

El estudio se realizó incluyendo pacientes procedentes de la base de datos CAPUCI I, reclutados desde el 01-01-2000 hasta el 28-02-2002, y CAPUCI II, que se realizó desde el 01-01-2008 hasta la actualidad. De cara al presente estudio, los pacientes introducidos en el análisis fueron reclutados desde el 01-01-2008 hasta el 30-04-2014.

Criterios de inclusión de los estudios CAPUCI I y II

Todos los pacientes con más de 18 años con diagnóstico de neumonía comunitaria grave admitidos en las UCIs, con fracaso de uno o más órganos.

Criterios de exclusión de los estudios CAPUCI I y II

Los pacientes diagnosticados de neumonía asociada a cuidados sanitarios fueron excluidos. También se excluyeron del estudio aquello pacientes en que la neumonía se consideraba un evento terminal, pacientes en programas de cuidados paliativos y pacientes con orden de no realizar RCP.

Recogida de información

Un investigador por cada centro participante en los estudios CAPUCI I y II recogió la información clínica. La recogida de información de los pacientes se llevó a cabo a través de las historias clínicas hospitalarias y documentos clínicos, a través de un protocolo de recogida de datos previamente definido. Los datos registrados en las base de datos CAPUCI I y II fueron similares. De forma esquemática las variables que se recogieron son:

- Datos demográficos: Datos de filiación y demográficos.
- Antecedentes patológicos: Historia de enfermedades antiguas y concomitantes y tratamientos médicos realizados anteriormente al ingreso.
- Datos de presentación clínica de la enfermedad:
    - Síndromes clásicos (neumonía bacteriana, viral o sin germen).

    - Complicaciones clínicas (insuficiencia respiratoria severa, shock séptico, insuficiencia renal, otras complicaciones clínicas menos frecuentes).
    - Patrón radiológico (neumonía unilateral, multilobar, bilateral, rápida extensión del infiltrado radiológico).
    - Escalas de gravedad el ingreso y de valoración pronóstica (APACHE II score en estudio CAPUCI I; SAPS III score, PSI y CURB-65 en estudio CAPUCI II).
    - Datos microbiológicos de la enfermedad (tipo y número de muestras respiratorias y sistémicas realizadas para realización del diagnóstico de neumonía).
- Datos sobre los tratamientos administrados: antibioticoterapia empírica, tipo y número de antibióticos administrados, tiempo pasado entre la administración de la primera dosis de antibiótico y la llegada a urgencias, cambio de antibiótico, duración del tratamiento antimicrobiano, uso de tratamientos coadyuvantes y necesidad de colocación de drenajes pleurales.
- Datos microbiológicos de la enfermedad: tipo de muestra en que se produce el aislamiento, número de muestras recogidas por cada paciente y sensibilidad antibiótica del microorganismo aislado.

Definiciones

Las definiciones se establecieron siguiendo los criterios establecidos en la literatura.

La neumonía comunitaria se diagnosticó cuando un paciente tenía un clínica compatible además de un nuevo infiltrado pulmonar en la radiografía de tórax (98). La neumonía comunitaria severa se definió

como aquella neumonía que requiere ingreso en UCI, por insuficiencia de uno o más órganos (99).

Cada paciente se consideraba fumador en caso de haber fumado más de un paquete al día en los últimos diez años (100). Se definió como dependencia del alcohol a cualquier paciente con un consumo diario de más de 80 g de alcohol cada día en los últimos 10 años (101).

Inmunosupresión fue definida como la presencia de una inmunodeficiencia primaria o de una inmunodeficiencia secundaria en contexto de radioterapia, uso de fármacos citotóxicos o esteroides (dosis diaria de más de 20 mg de prednisona o algún equivalente durante más de dos semanas), trasplante o síndrome de inmunodeficiencia adquirida (102).

El shock séptico se consideró cuando fue necesaria la administración de vasopresores durante más de cuatro horas para conseguir una presión arterial adecuada pese a la resucitación previa con sueroterapia (103). La insuficiencia respiratoria se definió como una saturación de oxígeno <90% a aire ambiente o una presión de oxígeno en sangre arterial en relación a la fracción inspirada de oxígeno (Pa02/FiO2) < 250 mmHg (104). La extensión radiográfica rápida se definió como un aumento del infiltrado de más del 50% tras 48 horas desde el ingreso (105).

Para la realización del diagnóstico microbiológico de neumonía se necesitaba un resultado microbiológico positivo obtenido a partir de por lo menos una de las muestras cursadas: aspirado traqueal, bronco-aspirado, lavado bronco-alveolar, cultivo de derrame pleural o hemocultivo; así mismo, la presencia de clínica compatible y la positividad del antígeno urinario para *Legionella pneumophila* o

Streptococcus pneumoniae condicionaban un diagnóstico de neumonía bacteriana.

Se consideró que un paciente recibió monoterapia o tratamiento antibiótico combinado en caso de recibir el mismo antibiótico (uno o más) durante las primeras 48 horas del ingreso en UCI.

Se consideró que un paciente recibió tratamiento antibiótico precoz en caso de recibir la primera dosis de antibiótico durante las primeras tres horas desde su llegada a urgencias.

Diseño del estudio

Análisis retrospectivo de dos cohortes recogidas prospectivamente en dos temporadas diferentes, realizándose posteriormente un estudio caso-control comparando pacientes de las dos cohortes.

Estudio caso-control

Para evaluar diferencias entre la población del estudio CAPUCI I y la población del estudio CAPUCI II, se realizó un estudio caso-control. Para la definición de los grupos a comparar se definieron los grupos CAPUCI I y CAPUCI II, que incluyen los pacientes de las bases de datos CAPUCI I y CAPUCI II que se introdujeron en el análisis caso-control.

Para la realización del apareamiento se recogieron todos los pacientes con diagnóstico microbiológico bacteriano confirmado pertenecientes a la base de datos CAPUCI II, y se buscó en la base datos del CAPUCI I cada individuo con infección por el mismo microorganismo y con las mismas características en las variables investigadas.

Se decidió utilizar una técnica exacta de apareamiento de casos y controles para minimizar el riesgo de sesgo de selección debido a las

diferencias entre grupos. En el caso de encontrar más individuos del grupo CAPUCI I con características similares al individuo de referencia del grupo CAPUCI II, se seleccionaba al azar uno de los individuos del grupo CAPUCI I. El número de pacientes a introducir en el estudio caso-control y la proporción de los diferentes microorganismos de la muestra no fueron establecidos a priori; se decidió buscar a todos los pacientes con características microbiológicas y clínicas entre la base de datos CAPUCI II y CAPUCI I.

Las variables empleadas para el apareamiento fueron las siguientes: microorganismo, presencia de shock, necesidad de ventilación mecánica invasiva (VMI), inmunosupresión, EPOC, edad.

Análisis estadístico

Para la realización del análisis estadístico se utilizó el programa de estadística IBM SPSS Statistics para Mac, versión 20.0 (SPSS, Chicago, IL).

Las variables categóricas se definieron como número de casos y proporción, y se compararon mediante la prueba de Chi-cuadrado o, en los casos que lo requerían, el Test Exacto de Fisher. Las variables continuas se definieron como mediana y rango intercuartil, y se compararon con la prueba T de Student o, en los casos necesarios con la prueba no paramétrica de U de Mann-Whitney. El porcentaje de cambio (razón de odds) en la incidencia se presentó asociado a su intervalo de confianza del 95%.

Para identificar variables asociadas de forma independiente a una diferente mortalidad se realizó un análisis multivariado mediante un modelo de regresión logística. Las variables que presentaron diferencias significativas en el análisis univariante fueron introducidas en el modelo

multivariado. Todos los análisis estadísticos se llevaron a cabo considerando un nivel de significación o valor de P menor de 0.05.

El método de Kaplan-Meier se utilizó para estimar el tiempo transcurrido desde el ingreso hasta el fallecimiento o el alta de la UCI y para comparar la supervivencia dependiendo de la administración de monoterapia o tratamiento combinado y de la administración precoz o tardía del tratamiento antibiótico. Las curvas de supervivencia fueron comparadas con el test de long-rank.

Confidencialidad de los datos y consentimiento informado

La recogida de datos se hizo con unos protocolos previamente establecidos y los datos se introdujeron en una base de datos con un sistema de codificación con el fin de proteger la información personal de cada paciente. En la hoja de recogida de datos el código se relacionó con el número de historia clínica. Estos datos son custodiados por el investigador responsable. El estudio fue aprobado por el Comité Ético del hospital coordinador (Hospital Joan XXIII; REF 2005/NA). El consentimiento informado no fue necesario dado el carácter observacional del estudio.

V. RESULTADOS

RESULTADOS

Partiendo de la hipótesis de trabajo, el estudio se llevó a cabo mediante la elaboración de dos trabajos diferentes, que tratan de dar respuesta a cada uno de los objetivos planteados. La exposición de los resultados se estructurará en dos partes, correspondientes a cada uno de los trabajos.

A continuación, y como parte final de la memoria, se añade en forma de apartado Anexo a varias publicaciones relacionadas que se llevaron a cabo antes y durante la elaboración del presente trabajo, consistentes en dos artículos originales y un artículo de revisión.

En el primer artículo original, titulado "Community-acquired *Legionella* Pneumonia in the intensive care unit: Impact on survival of combined antibiotic therapy", se realizó un estudio observacional comparando pacientes con neumonía grave por *Legionella pneumophila* y shock séptico secundario, confirmándose una disminución de la mortalidad tras administración de forma empírica de dos antibióticos.

En el segundo artículo original, titulado "Causes of non-adherence to therapeutic guidelines in severe community-acquired pneumonia", se exploran las causas de no adherencia a las recomendaciones internacionales a la hora de iniciar un tratamiento antibiótico empírico en pacientes con neumonía comunitaria grave bacteriana; el estudio se realizó a través de una encuesta realizada a médicos expertos en enfermedades infecciosas que trabajan en una UCI.

En el artículo de revisión, titulado "What is new in antibiotic therapy in community-acquired pneumonia? An evidence-based approach focusing on combined therapy", se realizó un repaso de todos los artículos publicados hasta Marzo 2015 que evalúan cambios en la mortalidad tras

administración de uno o dos antibióticos de forma empírica, en pacientes con neumonía comunitaria. Además, se explora si la administración de una específica familia de antibióticos –en monoterapia o en asociación con otra familia de antibióticos- se asocia a una mortalidad diferente.

Primer artículo original de la tesis

Estudio caso-control que evalúa cambios de mortalidad tras la administración de uno o dos antibióticos y de antibioticoterapia precoz o tardía, en una muestra de pacientes con neumonía grave neumocócica.

Artículo

Gattarello S, Borgatta B, Solé-Violan J, Vallés J, Vidaur L, Zaragoza R, Torres A, Rello J. "Decrease in mortality in severe community-acquired pneumococcal pneumonia: impact of improving antibiotic strategies (2000-2013)". Chest. 2014; 146: 22-31.

Segundo artículo original de la tesis

Estudio caso-control que evalúa cambios de mortalidad tras la administración de uno o dos antibióticos y de antibioticoterapia precoz o tardía, en una muestra de pacientes con neumonía grave bacteriana no neumocócica.

Artículo

Gattarello S, Lagunes L, Vidaur L, Solé-Violan J, Zaragoza R, Vallés J, Torres A, Sierra R, Sebastian R, Rello J. "Improvement of Antibiotic Therapy and ICU Survival in Severe Non-Pneumococcal Community-

Acquired Pneumonia: a Matched Case-Control Study". Critical Care. 2015; 19: 335.

Tercer artículo original (Anexo)

Estudio observacional que evalúa cambios de mortalidad tras la administración de uno o dos antibióticos en una muestra de pacientes con neumonía grave por *Legionella pneumophila*.

Artículo

Rello J, Gattarello S, Souto J, Solé-Violan J, Valles J, Peredo R, Zaragoza R, Vidaur L, Parra A, Roig J. "Community-acquired *Legionella* Pneumonia in the intensive care unit: Impact on survival of combined antibiotic therapy". Medicina Intensiva. 2013; 37: 320-326.

Cuarto artículo original (Anexo)

Estudio observacional en forma de encuesta clínica que evalúa las causas de no adherencia a las recomendaciones internacionales a la hora de iniciar un tratamiento antibiótico empírico en caso de neumonía comunitaria grave.

Artículo

Gattarello S, Ramírez S, Almarales JR, Borgatta B, Lagunes L, Encina B, Rello J. "Causes of non-adherence to therapeutic guidelines in severe community-acquired pneumonia". Revista Brasileira de Terapia Intensiva. 2015; 27: 44-50.

Artículo de revisión (Anexo)

Revisión de todos los artículos científicos publicados desde 2005 hasta 2015 que exploran los desenlaces clínicos tras la administración de uno o dos antibióticos y dependiendo de la familia de antibiótico que se administró.

Artículo:

Gattarello S. “What is new in antibiotic therapy in community-acquired pneumonia? An evidence-based approach focusing on combined therapy”. Current Infection Disease Reports. 2015; 17: 501.

CHEST

Decrease in Mortality in Severe Community-Acquired Pneumococcal Pneumonia

Impact of Improving Antibiotic Strategies (2000-2013)

*Simone Gattarello, MD; Bárbara Borgatta, MD; Jordi Solé-Violán, MD, PhD; Jordi Vallés, MD, PhD; Loreto Vidaur, MD; Rafael Zaragoza, MD, PhD; Antoni Torres, MD, PhD; and Jordi Rello, MD, PhD; for the Community-Acquired Pneumonia en la Unidad de Cuidados Intensivos II Study Investigators**

OBJECTIVE: The objective of the present study was to compare antibiotic prescribing practices and survival in the ICU for patients with pneumococcal severe community-acquired pneumonia (SCAP) between 2000 and 2013.

METHODS: This was a matched case-control study of two prospectively recorded cohorts in Europe. Eighty patients from the Community-Acquired Pneumonia en la Unidad de Cuidados Intensivos (CAPUCI) II study (case group) were matched with 80 patients from CAPUCI I (control group) based on the following: shock at admission, need of mechanical ventilation, COPD, immunosuppression, and age.

RESULTS: Demographic data were comparable in the two groups. Combined antibiotic therapy increased from 66.2% to 87.5% ($P < .01$), and the percentage of patients receiving the first dose of antibiotic within 3 h increased from 27.5% to 70.0% ($P < .01$). ICU mortality was significantly lower (OR, 0.82; 95% CI, 0.68-0.98) in cases, both in the whole population and in the subgroups of patients with shock (OR, 0.67; 95% CI, 0.50-0.89) or receiving mechanical ventilation (OR, 0.73; 95% CI, 0.55-0.96). In the multivariate analysis, ICU mortality increased in patients requiring mechanical ventilation (OR, 5.23; 95% CI, 1.60-17.17) and decreased in patients receiving early antibiotic treatment (OR, 0.36; 95% CI, 0.15-0.87) and combined therapy (OR, 0.19; 95% CI, 0.07-0.51).

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

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ABBREVIATIONS: CAP = community-acquired pneumonia; IQR = interquartile range; SCAP = severe community-acquired pneumonia

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Community-acquired pneumonia (CAP) is a major health problem associated with high morbidity and mortality.[1,2] Despite geographic differences, *Streptococcus pneumoniae* is the most common cause of pneumonia worldwide.[1] Over the years, CAP studies have focused on risk factors,[3] microbiology,[4,5] biomarkers,[6,7] and mortality[8]; more recently, they have addressed the introduction of new antibiotic policies and the availability of new drugs.[9,10]

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

FOR EDITORIAL COMMENT SEE PAGE 6

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

Materials and Methods

This was a matched case-control study of two cohorts of patients prospectively recorded in Europe (the Community-Acquired Pneumonia en la Unidad de Cuidados Intensivos [CAPUCI] studies). CAPUCI I and II are two European, prospective, multicenter studies conducted in patients admitted to the ICU for CAP. The CAPUCI I study recorded data from 33 hospitals from 2000 to 2002. Data from this cohort have been reported elsewhere.[11] The CAPUCI II study was a follow-up project endorsed by the European Critical Care Research Network. Data were recorded from patients admitted for SCAP from 2008 to 2013 in 29 European ICUs. Demographic data, and clinical presentation, outcome, and antibiotic therapy data were registered; antibiotic prescription was left to the discretion of the attending physician. Patients were admitted to the ICU either to undergo mechanical ventilation or because they were critically ill,[21] in accordance to Infectious Disease Society of America/American Thoracic Society guidelines.[1] People with severe chronic illness in whom pneumonia was an expected terminal event were not included; patients were observed until ICU discharge or death. The study was approved by the ethics board of the coordinating center (REF 2005/NA), in accordance with national regulations, and informed consent was waived due to the observational nature of the studies. Definitions are given in e-Appendix 2.

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

Continuous variables were compared with Student t test for normally distributed variables, or the Mann-Whitney U test for nonnormally distributed variables. Categorical variables were evaluated with the χ^2 or two-tailed Fisher exact test. Results are expressed as median and interquartile range (IQR) for continuous variables or as percentages of the group from which they were derived for categorical variables. Two-tailed tests were used to determine statistical significance; a P value $< .05$ was considered significant.

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

Results

One hundred and sixty patients were enrolled: 80 patients from the 2008 to 2013 cohort (case group) paired with 80 from the 2000 to 2002 cohort (control group). Figure 1 shows the algorithm for the selection of the patients and the ICU mortality for each subgroup; incidence of severe pneumococcal pneumonia increased significantly (43.9% vs 27.0%; OR, 1.30; 95% CI, 1.15-1.48). Table 1 shows the variables used to match patients. The groups presented identical prevalence of the items evaluated: Shock at ICU admission was present in 60.0% of patients, while 65.0% had received mechanical ventilation. Thirty-three percent of patients were aged >65 years, 32.2% received a diagnosis of COPD, and 7.5% presented immunosuppression. The cause of immunosuppression was HIV infection in seven of 12 patients.

Medical history and clinical presentation were comparable in the two cohorts (Table 2). Estimated probability of death was 31.0% in the case group and 24.0% in the control group ($P = .35$). ICU length of stay was similar: Median (IQR) was 10.0 days (4-19) vs 10.0 days (4-17.8), respectively ($P = .97$). Blood cultures were positive in 36.2% of the case group and 40.0% of the

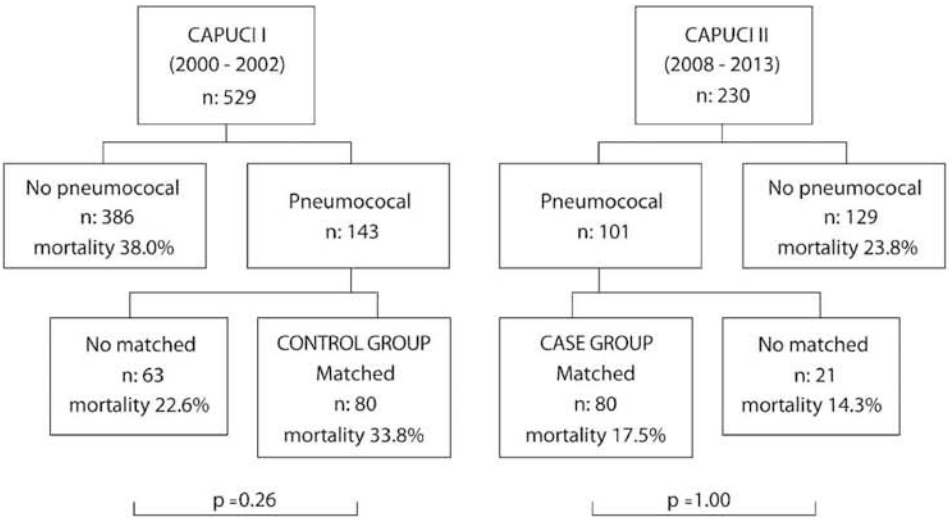

Figure 1 – *Flow diagram of patient selection and mortality in the different subgroups. CAPUCI = Community-Acquired Pneumonia en la Unidad de Cuidados Intensivos.*

control group ($P = .75$). As shown in Table 3, bacteremia was significantly associated with the presence of septic shock ($P = .05$). Acute kidney injury was observed in 44 patients (55.0%) in the case group vs 31 (39.2%) in the control group ($P = .06$), while rapid radiographic spread was recorded in 48.8% and 51.2%, respectively ($P = .87$).

ICU mortality was significantly different between the groups: 14 patients (17.5%) from the case group died compared with 27 (32.5%) in the control group, with an OR of ICU mortality of 0.82 (95% CI, 0.68-0.98; $P = .04$). Most deaths were late and due to multiorgan dysfunction syndrome. Figure 1 shows ICU mortality of the different subgroups. Mortality was comparable between matched and nonmatched patients in CAPUCI I (22.6% vs 33.8%, $P = .26$) and in CAPUCI II (17.5% vs 14.3%, $P = 1.00$). Figure 2 shows changes in ICU mortality between the two time periods in the whole population and in the subgroups of patients with shock (OR, 0.67; 95% CI, 0.50-0.89) and those receiving mechanical ventilation (OR, 0.73; 95% CI, 0.55-0.96). Kaplan-Meier survival analysis was performed in the global cohort and in the subgroups of patients with shock and under mechanical ventilation, stratifying by monotherapy vs combined therapy (log-rank $P < .01$, .02, and .01, respectively) (Fig 3) and early vs non-early antibiotic treatment (log-rank $P < .01$, .01, and .02, respectively) (Fig 4).

Combined therapy differed significantly between the groups: 70 patients (87.5%) from the case group received combined therapy vs 53 (66.2%) from the control group ($P < .01$) (Table 4). The first dose of antibiotic was administered within 3 h of admission to the ED in 70.0% of the case group but in only 27.5% of the control group ($P < .01$). Compliance with 2007 Infectious Disease Society of America/American Thoracic Society guidelines[1] was obtained in 64 patients (80.0%) in the case group and in 38 (47.5%) in the control group ($P < .01$).

The most frequent pattern of antibiotic use was a combination of a cephalosporin with a macrolide (Table 5), which was administered in 65 patients (40.6%): 38

TABLE 1] Description of Matched Variables

Variables	Case Group (n = 80)	Control Group (n = 80)
Age > 65 y	27 (33.8)	27 (33.8)
COPD	25 (32.2)	25 (32.2)
Immunosuppression	6 (7.5)	6 (7.5)
Shock at ICU admission	48 (60.0)	48 (60.0)
Invasive mechanical ventilation	52 (65.0)	52 (65.0)

Data are given as No. (%).

TABLE 2] Other Demographics Data and Clinical Presentations

Variable	Case Group (n = 80)	Control Group (n = 80)	*P* Value
Age, median (IQR), y	58.0 (46.0-69.8)	57.0 (48.0-70.8)	.99
Age < 50 y	30 (37.5)	23 (28.7)	.31
Age 50-64 y	23 (28.7)	28 (35.0)	.50
Age 65-74 y	15 (18.8)	15 (18.8)	1.00
Age ≥ 75 y	12 (15.0)	14 (17.5)	.42
Male sex	50 (62.5)	59 (73.8)	.17
Active smoker	39 (48.8)	38 (48.7)	1.00
Alcohol use	20 (25.0)	26 (33.3)	.30
Overweight	8 (10.7)	7 (8.8)	.79
Diabetes mellitus	9 (16.4)	18 (22.5)	.51
Cardiac failure	16 (20.0)	16 (20.0)	1.00
Cerebral vascular disease	6 (7.5)	8 (14.0)	.26
Malignancy	3 (3.8)	3 (3.8)	1.00
Estimated probability of death, median (IQR)	31.0 (17.0-52.0)	24.0 (24.0-40.0)	.35
ICU length of stay, median (IQR), d	10.0 (4.0-19.0)	10.0 (4.0-17.8)	.97
Mechanical ventilation, median (IQR), d	7.0 (2.8-18.8)	7.5 (3.0-17.8)	.99
Bacteremia	29 (36.2)	32 (40.0)	.75
Acute kidney injury	44 (55.0)	31 (39.2)	.06
Rapid radiographic spread	39 (48.8)	41 (51.2)	.87
ICU mortality	14 (17.5)	26 (32.5)	.04

Data given as No. (%) unless otherwise indicated. IQR = interquartile range.

(47.5%) in the case group and 27 (33.8%) in the control group ($P = .11$). The most frequent combination in the case group was ceftriaxone and azithromycin (26 patients, 32.5%), while in the control group it was ceftriaxone and clarithromycin (20 patients, 25.0%). The second most frequently administered antibiotic pattern was a cephalosporin and a quinolone; cefotaxime/ceftriaxone plus levofloxacin was the most used combination (case group: 24 patients [30.0%]; control group: nine patients [11.3%]).

TABLE 3] Comparison Between Bacteremic and Nonbacteremic Patients

Variable	Bacteremia (n = 61)	No Bacteremia (n = 99)	*P* Value
Age, median (IQR), y	55.0 (46.5-64.5)	57.0 (46.3-70.0)	.18
Nonimmunocompromised	54 (88.5)	94 (94.9)	.22
Immunocompromised: HIV	5 (8.2)	4 (4.0)	1.00
Immunocompromised: non-HIV	2 (3.3)	1 (1.0)	1.00
Shock at ICU admission	43 (70.5)	53 (53.5)	.05
Invasive mechanical ventilation	42 (68.9)	62 (62.6)	.50
Acute kidney injury	31 (50.8)	44 (44.4)	.42
Rapid radiographic spread	33 (54.1)	47 (47.5)	.52
Combined therapy	47 (77.1)	76 (76.8)	1.00
AB initiated within 0-3 h	29 (47.5)	49 (49.5)	.87
ICU mortality	15 (24.6)	25 (25.3)	1.00

Data given as No. (%) unless otherwise indicated. AB = antibiotic. See Table 2 legend for expansion of other abbreviation.

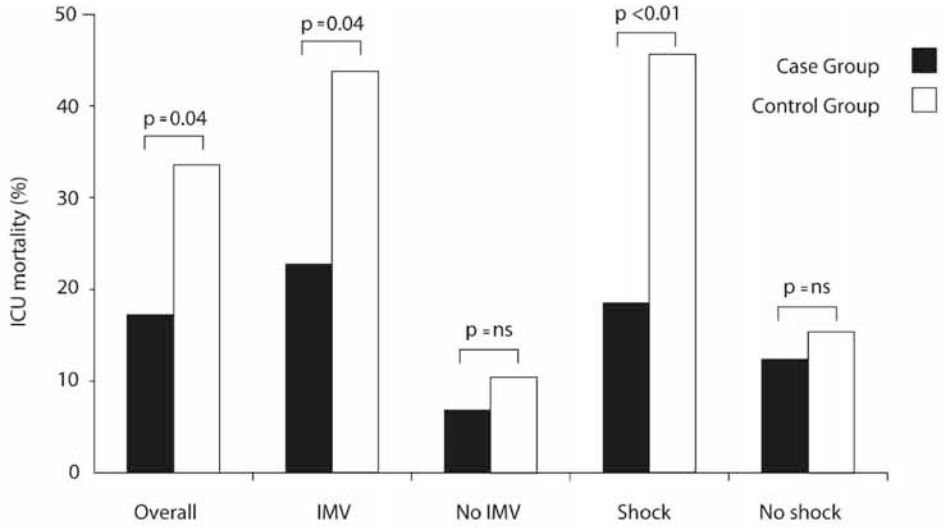

Figure 2 – *ICU mortality in the whole population and in different subgroups of patients. IMV = invasive mechanical ventilation.*

Table 6 shows the univariate analysis for determining variables associated with ICU mortality. COPD ($P = .05$), estimated probability of death ($P < .01$), shock at ICU admission ($P < .01$), invasive mechanical ventilation ($P < .01$), acute kidney injury ($P = .02$), rapid radiographic spread ($P = .02$), combined therapy ($P = .02$), and early antibiotic administration ($P = .02$) differed significantly between survivors and nonsurvivors.

Multivariate analysis was performed to identify risk factors for mortality (Table 7). Variables with significant differences from the univariate model (Table 6) were introduced in this model. The need for invasive mechanical ventilation was associated with a higher risk of ICU mortality (OR, 5.23; 95% CI, 1.60-17.17). In contrast, first dose of antibiotic within 3 h (OR, 0.36; 95% CI, 0.15-0.87) and combined therapy (OR, 0.19; 95% CI, 0.07-0.51) were associated with a lower risk of ICU mortality in pneumococcal SCAP. The model remained similar when the variable "macrolide use" was added as a dependent variable in the multivariate analysis (macrolide use OR for death, 1.52; 95% CI, 0.56-4.16).

Discussion

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

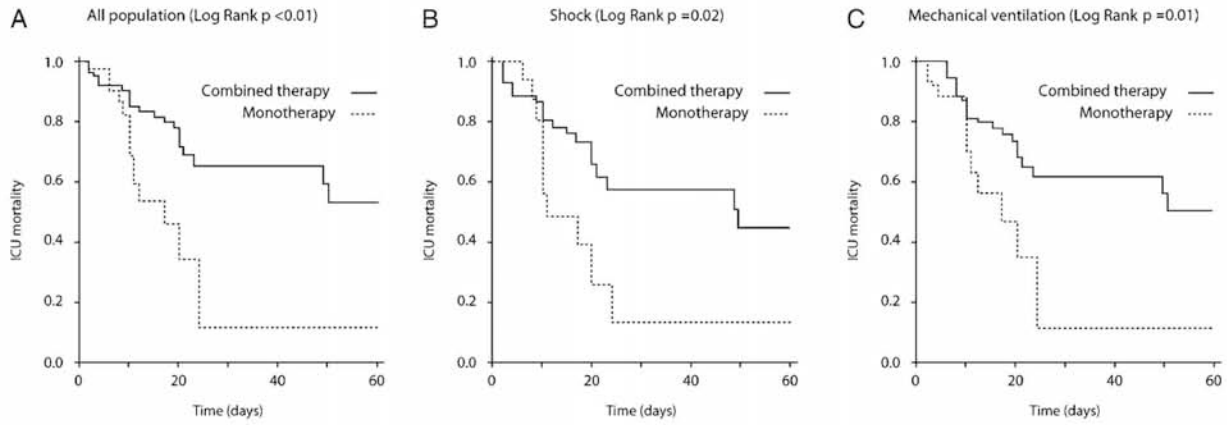

Figure 3 – *Kaplan-Meier survival curve stratified for monotherapy vs combined therapy. A, The whole population. B, Patients with shock. C, Patients receiving mechanical ventilation.*

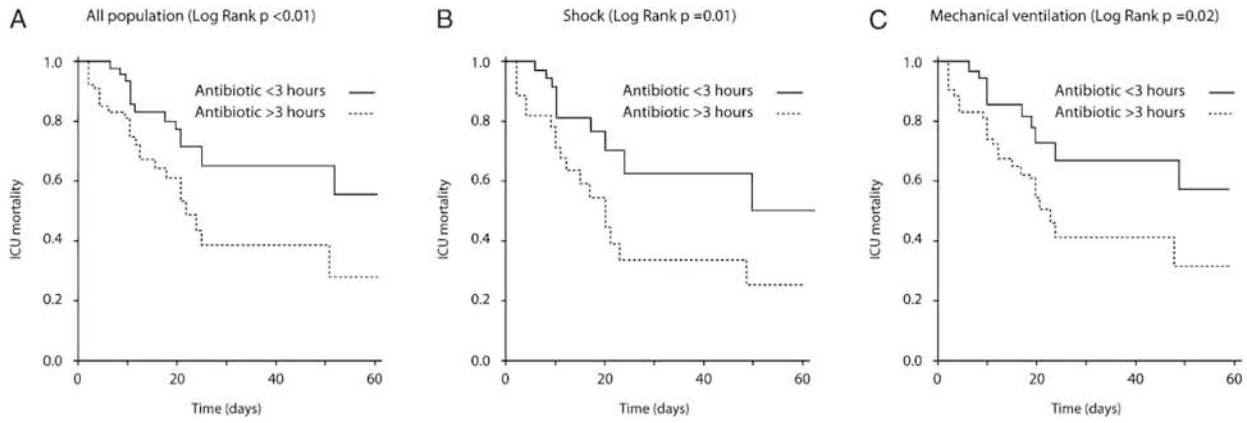

Figure 4 – *Kaplan-Meier survival curve stratified for early vs nonearly antibiotic treatment. A, The whole population. B, Patients with shock. C, Patients receiving mechanical ventilation.*

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

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

Studies showing that early antibiotic administration seems to be unrelated to better outcomes did not differentiate between critical and noncritical patients.[41,42] It has consistently been demonstrated that early antibiotic administration is a determinant of the outcome in severe sepsis and shock, regardless the source of infection,[38-40] supporting the 2012 Surviving Sepsis Campaign's recommendation on initiation of antibiotics within the first hour of the diagnosis of severe sepsis.[35]

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

Still, it is unclear why combined therapy is superior to monotherapy. Possible reasons include coverage of atypical pathogens, greater probability of covering

TABLE 4] Characteristics of Antibiotic Treatment

Characteristics	Case Group (n = 80)	Control Group (n = 80)	*P* Value
Previous AB	10 (12.5)	7 (8.8)	.61
Monotherapy	10 (12.5)	27 (33.8)	<.01
Combined therapy	70 (87.5)	53 (66.2)	<.01
AB initiated within 0-3 h	56 (70.0)	22 (27.5)	<.01
AB initiated within 4-6 h	16 (20.0)	26 (32.5)	.11
AB initiated at >6 h	8 (10.0)	32 (40.0)	<.01
Adequate according to 2007 IDSA/ATS guidelines	64 (80.0)	38 (47.5)	<.01

Data given as No. (%) unless otherwise indicated. IDSA/ATS = Infectious Diseases Society of America/American Thoracic Society. See Table 3 for expansion of other abbreviation.

TABLE 5] Most Frequent Patterns of Antibiotic Treatment

Antibiotic Treatment	All Patients (N = 160)	Case Group (n = 80)	Control Group (n = 80)	*P* Value[a]
Cephalosporin and macrolide	65 (40.6)	38 (47.5)	27 (33.8)	.11
Ceftriaxone/cefotaxime and azithromycin	26 (16.2)	26 (32.5)	0 (0)	<.01
Ceftriaxone/cefotaxime and clarithromycin	30 (18.8)	10 (12.5)	20 (25.0)	.07
Other cephalosporin and macrolide	9 (5.6)	2(2.5)	7 (8.8)	.17
Cephalosporin and quinolone	37 (23.1)	26 (32.5)	11 (13.8)	<.01
Cefotaxime/ceftriaxone and levofloxacin	33 (20.6)	24 (30.0)	9 (11.3)	<.01
Other cephalosporin and quinolone	4 (2.5)	2 (2.5)	2 (2.5)	1.00
Ceftriaxone/cefotaxime	15 (9.4)	4 (5.0)	11 (13.8)	.10
Levofloxacin	11 (6.9)	5 (6,2)	6 (7.5)	1.00
Miscellaneous combined therapy	21 (13.1)	6 (7.5)	15 (18.8)	.06
Miscellaneous monotherapy	11 (6.9)	1 (1.3)	10 (12.4)	<.01
Overall	160 (100)	80 (100)	80 (100)	...

Data given as No. (%) unless otherwise indicated.
[a]*P* value calculated between case group and control group.

multiresistant microorganisms, synergies, and antiinflammatory and immunomodulatory effects of some antimicrobials. In the present study, as all cases were caused by *S pneumoniae*, it is reasonable to assume that factors other than covering atypical pathogens or covering multiresistant microorganisms were related to decreased mortality.

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

TABLE 6] Univariate Analysis to Assess Risk Factors for ICU Mortality Due to Pneumococcal SCAP

Risk Factor	Survival (n = 120)	No Survival (n = 40)	OR (95% CI)	*P* Value
Age >65 y	37 (30.8)	17 (42.5)	1.20 (0.90-1.61)	.18
Overweight	11 (9.4)	4 (10.5)	1.01 (0.90-1.15)	.76
Alcohol use	31 (26.3)	15 (37.5)	1.18 (0.91-1.54)	.23
Active smoker	53 (44.9)	24 (60.0)	1.38 (0.91-2.1)	.10
Diabetes mellitus	19 (19.6)	8 (21.1)	1.02 (0.84-1.23)	.82
Cardiomyopathy	23 (19.2)	9 (22.5)	1.04 (0.86-1.26)	.65
COPD	32 (26.7)	18 (45.0)	1.33 (1.00-4.73)	.05
Immunosuppression	7 (5.8)	5 (12.5)	1.08 (0.95-1.22)	.18
Estimated probability of death, median (IQR)	24 (14-40)	40 (24-52)	...	<.01
Shock at ICU admission	65 (54.2)	31 (77.5)	2.04 (1.11-3.74)	<.01
Invasive mechanical ventilation	69 (57.5)	35 (87.5)	3.4 (1.46-7.92)	<.01
Acute kidney injury	50 (41.7)	25 (64.1)	1.63 (1.04-2.54)	.02
Rapid radiographic spread	53 (44.2)	27 (67.5)	1.72 (1.07-2.76)	.02
Combined therapy	98 (81.7)	25 (62.5)	0.49 (0.28-0.85)	.02
AB initiated within 0-3 h	65 (54.2)	13 (32.5)	0.41 (0.19-0.87)	.02

Data given as No. (%) unless otherwise indicated. SCAP = severe community-acquired pneumonia. See Table 2 and 3 legends for expansion of other abbreviations.

TABLE 7] Multivariate Analysis to Assess Risk Factors for ICU Mortality Due to SCAP

Variable	OR (95% CI)	*P* Value
Invasive mechanical ventilation	5.23 (1.60-17.17)	< .01
Rapid radiographic spread	2.22 (0.91-5.43)	.81
Acute kidney injury	2.09 (0.76-5.79)	.15
COPD	1.78 (0.72-4.36)	.21
Shock at ICU admission	1.52 (0.52-4.49)	.45
Estimated probability of death	1.00 (0.98-1.03)	.81
AB initiated within 3 h	0.36 (0.15-0.87)	.02
Combined therapy	0.19 (0.07-0.51)	< .01

See Table 3 and 6 legends for expansion of abbreviations.

A significant decrease in mortality was observed in the whole population as well as in the subgroups of patients with shock and receiving mechanical ventilation (Fig 2), even when stratified according to combined antibiotic therapy vs monotherapy (Fig 3) and early antibiotic treatment vs non-early antibiotic administration (Fig 4). This observation is not only of academic interest: In view of these results, all patients with pneumococcal SCAP requiring ICU admission should receive early treatment and combined antibiotic therapy.

Significant differences in antibiotic regimens administered to the study groups were seen (Table 5), the most important being that azithromycin was not administered to the control group, because it was not available in IV formulation in Spain at the time of the CAPUCI I study. Also, more broad-spectrum antibiotic combinations were administered in the control group than in the case group; in the case group, 80.0% of patients received a combination of cephalosporin plus a macrolide or fluoroquinolone compared with 47.6% of control subjects, suggesting a higher compliance to guidelines in the case group. No differences in mortality were found between different antibiotic regimens.

Interestingly, our study population comes from a large, prospective, multicenter database and is homogeneous, since all the patients were admitted to the ICU. To our knowledge, this is the first study to compare the clinical characteristics of the subset of critically ill patients in the ICU with pneumococcal CAP. Moreover, whereas most prior studies evaluating antibiotic treatment in SCAP have been limited to subgroups with shock, our results showed a lower mortality rate in different populations, stressing the clinical implications of our findings.

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

Another important limitation is that several improvements have been introduced in the management of critical patients, including management of septic shock and mechanical ventilation. Even though major determinants of mortality for SCAP were included in our analysis, it was not possible to record all of these changes. Severity of illness was recorded with different scores; therefore, univariate and multivariate analysis adjusted severity for the "estimated risk of death" rather than a score. We acknowledge that the use of matching criteria for respiratory failure other than mechanical ventilation, such as Pao_2/Fio_2, may be associated with different outcomes, but this may also be influenced by other supporting measures like positive end-expiratory pressure level or other ventilator settings. Bacteremia alone is not a good tool to predict outcome in pneumococcal pneumonia[51]; for this reason, this variable was not used to match cohorts. Although reports[47-49] have correlated variation in serotypes with outcomes and complications, data regarding vaccination or serotypes were not recorded in our study. Finally, a selection bias may limit the generalization of findings.

Conclusions

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

Acknowledgments

Author contributions: S. G. served as principal author, had full access to all of the data in the study, and takes responsibility for the integrity of the data and the accuracy of the data analysis. S. G. and J. R. contributed to the study concept and design; B. B., J. S.-V., J. V., L. V., R. Z., and A. T. contributed to data interpretation; S. G. and J. R. contributed to drafting of the manuscript; B. B., J. S.-V., J. V., L. V., R. Z., and A. T. contributed to critical revision of the manuscript; and B. B., J. S.-V., J. V., L. V., R. Z., and A. T. contributed to approval of the final version.

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Additional information: The e-Appendixes can be found in the Supplemental Materials section of the online article.

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CRITICAL CARE

RESEARCH Open Access

Improvement of antibiotic therapy and ICU survival in severe non-pneumococcal community-acquired pneumonia: a matched case–control study

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Abstract

Introduction: We aimed to compare intensive care unit mortality due to non-pneumococcal severe community-acquired pneumonia between the periods 2000–2002 and 2008–2014, and the impact of the improvement in antibiotic strategies on outcomes.

Methods: This was a matched case–control study enrolling 144 patients with non-pneumococcal severe pneumonia: 72 patients from the 2000–2002 database (CAPUCI I group) were paired with 72 from the 2008–2014 period (CAPUCI II group), matched by the following variables: microorganism, shock at admission, invasive mechanical ventilation, immunocompromise, chronic obstructive pulmonary disease, and age over 65 years.

Results: The most frequent microorganism was methicillin-susceptible *Staphylococcus aureus* (22.1 %) followed by *Legionella pneumophila* and *Haemophilus influenzae* (each 20.7 %); prevalence of shock was 59.7 %, while 73.6 % of patients needed invasive mechanical ventilation. Intensive care unit mortality was significantly lower in the CAPUCI II group (34.7 % versus 16.7 %; odds ratio (OR) 0.78, 95 % confidence interval (CI) 0.64–0.95; $p = 0.02$). Appropriate therapy according to microorganism was 91.5 % in CAPUCI I and 92.7 % in CAPUCI II, while combined therapy and early antibiotic treatment were significantly higher in CAPUCI II (76.4 versus 90.3 % and 37.5 versus 63.9 %; $p < 0.05$). In the multivariate analysis, combined antibiotic therapy (OR 0.23, 95 % CI 0.07–0.74) and early antibiotic treatment (OR 0.07, 95 % CI 0.02–0.22) were independently associated with decreased intensive care unit mortality.

Conclusions: In non-pneumococcal severe community-acquired pneumonia , early antibiotic administration and use of combined antibiotic therapy were both associated with increased intensive care unit survival during the study period.

Introduction

In Western countries, community-acquired pneumonia (CAP) is the leading cause of death and is associated with high healthcare costs [1]. In the intensive care unit (ICU) setting, it is one of the most common reasons for admission and the most frequent causes of mortality [2]. Antibiotic treatment is the cornerstone for management of pneumonia, and adequate empiric treatment is associated with improved outcomes [1].

The trend in CAP mortality over recent decades remains unclear, despite many efforts to identify it. Contrasting results have been obtained in different publications because most of them did not differentiate between outpatients, patients admitted to the ward and patients admitted to the ICU [3, 4]. Conversely, many recently published studies have found a significant decrease in mortality in septic shock [5–7], or in severe respiratory failure requiring invasive mechanical ventilation (IMV) [8]; therefore, it is reasonable to assume that mortality due to severe pneumonia, especially when complicated with septic shock, may have decreased in the last few years. In a recent study, we found a reduction in mortality due to pneumococcal severe

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(S)CAP and an association between better management of antibiotic therapy and improved ICU survival [9].

The present study hypothesizes that, as in pneumococcal SCAP [9], an improvement in antibiotic policies will contribute to reducing mortality in non-pneumococcal SCAP. The primary objective was to determine ICU mortality due to non-pneumococcal SCAP, and the secondary objective was to assess whether improvements in antibiotic prescription had been implemented.

Materials and methods

This was a matched case–control study enrolling 144 ICU patients diagnosed with non-pneumococcal SCAP: 72 patients from the CAPUCI I study (2000–2002 period) were paired with 72 patients from the CAPUCI II database (2008–2014 period).

CAPUCI I was a multicenter, prospective, observational study carried out in 33 hospitals in Spain between 2000 and 2002. All patients admitted to ICU with diagnosis of SCAP were included. CAPUCI II was a follow-up project endorsed by the European Critical Care Research Network, carried out in 29 European ICUs from 2008 to 2014. In both studies, patients were admitted to the ICU either to undergo IMV or because they were in an unstable clinical condition [1]. All cases were followed until ICU discharge or death, and all clinical decisions were left to the discretion of the attending physician. Data from these cohorts have been reported elsewhere [10]. The Joan XXIII University Hospital Ethics Board (coordinating centre) approved the study (REF 2005/NA); the need for informed consent was waived due to the observational nature of the studies.

Pneumonia was diagnosed when a patient had consistent clinical findings plus a new pulmonary infiltrate on chest radiography. Immunocompromise was defined as primary immunodeficiency or immunodeficiency secondary to radiation treatment, use of cytotoxic drugs or steroids (daily doses >20 mg prednisolone or equivalent for >2 weeks), transplantation or AIDS. Shock was defined as the need for a vasopressor during >4 hours after fluid replacement; rapid radiographic spread was defined as an increase in the size of opacities on chest radiograph >50 % at 48 hours.

SCAP was defined as pneumonia that required ICU admission, with single or multi-organ failure. Patients proceeding from a long-term care facility, diagnosed with healthcare-associated pneumonia and with a no-cardiopulmonary resuscitation indication were not included. Microbiological diagnosis required a positive result from a respiratory sample or blood culture, or a positive urinary antigen in the case of *Legionella* spp. infection. Probability of death was predicted according to the "estimated risk of mortality" using the Acute Physiology and Chronic Health Evaluation (APACHE) II score in the CAPUCI I cohort and Simplified Acute Physiology Score (SAPS) III in the CAPUCI II cohort [11, 12]. Monotherapy and combined therapy were defined as administration of the same antibiotic (one or more) during the first 2 days of ICU admission. Early antibiotic administration was defined as administration of the first dose of antibiotic within 3 hours of hospital admission.

Patients with pneumonia and negative cultures, documented viral pneumonia or mixed aerobic/anaerobic flora were excluded; likewise, aspiration pneumonia, often associated with impaired clinical status [13], was excluded from the analysis so as to avoid bias. To perform the case–control analysis, each patient from the CAPUCI II group with a confirmed microbial etiology was matched with one from the CAPUCI I group with the same microorganism. Subsequently, the rest of variables used to match patients were: 1) presence of shock at ICU admission; 2) need for IMV; 3) immunosuppression; 4) chronic obstructive pulmonary disease; and 5) age (cut-off, 65 years) [14]; all main determinants for mortality in CAP [15, 16].

All data management and statistical analyses were performed using the SPSS 20 processor (SPSS inc., Chicago, IL). Results are expressed as medians and interquartile range for continuous variables, or as absolute percentages for categorical variables. Continuous variables were compared with the Mann–Whitney U test (non-normally distributed variables). Categorical variables were assessed with the chi-square or two-tailed Fisher exact test.

A multivariate model was performed to identify the variables associates with changes in mortality. To construct the model, we performed a logistic regression using all variables from the univariate analysis that were associated with a different mortality as covariates; subsequently, to optimize the model and minimize an overfitting bias, an automatic stepwise backward covariate selection was performed. Thus, multivariate analysis was finally adjusted according to the following variables: shock at admission, acute renal failure, combination therapy and early antibiotic administration.

Kaplan-Meier analysis was used to construct survival curves for patients receiving combination and monotherapy regimens and early versus late antibiotic administration.

Results

ICU mortality was significantly lower in the CAPUCI II group (34.7 versus 16.7 %; odds ratio (OR) 0.78, 95 % confidence interval (CI) 0.64–0.95; $p = 0.02$). Figure 1 shows a flow chart analysis for patient selection; in both CAPUCI I and CAPUCI II populations, mortality among patients enrolled in the analysis was compared with mortality of the rest of patients in the same group, with no significant differences being found (Fig. 1). In both cohorts, mortality of patients enrolled in the case–control analysis did not present significant differences when compared with patients not introduced into the analysis. Mortality in the

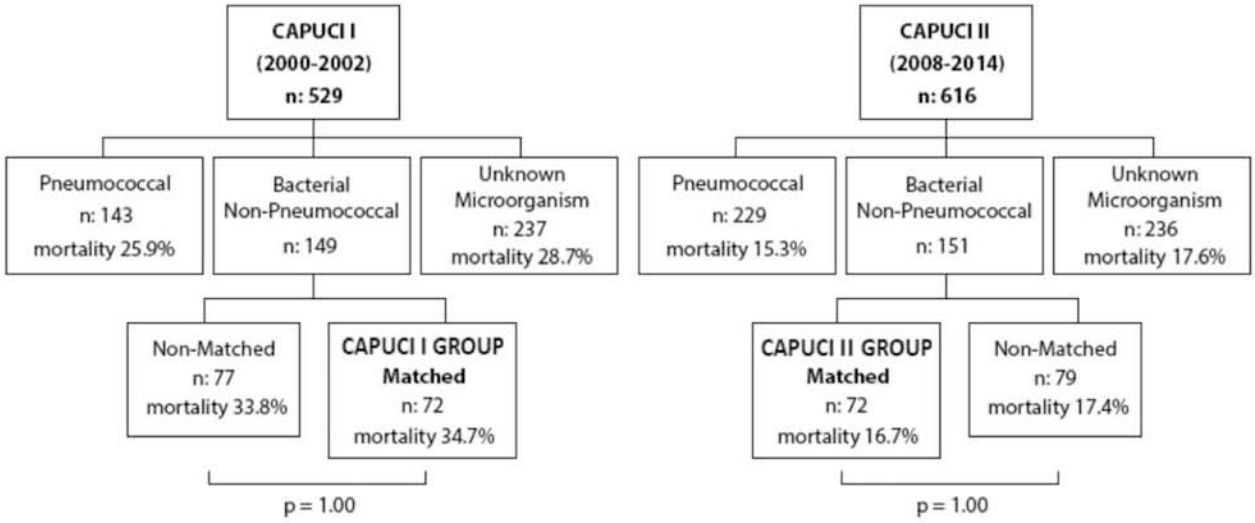

Fig. 1 Flow chart diagram of patient selection and mortality in the different subgroups

CAPUCI I cohort was 34.7 % in patients enrolled in the analysis versus 33.8 % in non-matched patients with non-pneumococcal pneumonia with confirmed microorganism (p = 1.00); in CAPUCI II, it was 16.7 % in matched and 17.4 % in non-matched patients, respectively (p = 1.00). Figure 2 depicts survival depending on the microbiological isolate: the most frequent microorganism was *Staphylococcus aureus* (22.1 %), followed by *Legionella pneumophila* and *Haemophilus influenzae* (each 20.7 %). Table 1 shows the variables used to pair patients; individuals selected for the case–control analysis showed a prevalence of shock and IMV of 59.7 % and 73.6 %, respectively. Furthermore, Table 1 shows the prevalence of the matching variables in patients with non-pneumococcal bacterial pneumonia not selected for the matching analysis; no significant differences were observed between matched and non-matched patients. As indicated in Table 2, estimated probability of death was 32.0 % in the CAPUCI II group and 34.0 % in the CAPUCI I group (p = 0.59). Bacteremia was observed in 22.2 % of CAPUCI I and in 30.6 % of CAPUCI II (p = 0.35). No significant differences were observed in length of ICU stay (10.5 versus 12.0 days; p = 0.16) or length of IMV (8.0 versus 10.5 days; p = 0.18). Mortality showed an absolute reduction of 18 % between the CAPUCI II group (34.7 %) and the CAPUCI I group (16.7 %) (p = 0.02). Figure 3 compares ICU mortality between groups. In the CAPUCI II group, it fell significantly in the overall population with an OR of 0.78 (95 % CI 0.64–0.95; p = 0.02); in ventilated patients the OR was 0.70 (95 % CI 0.53–0.91; p = 0.01)

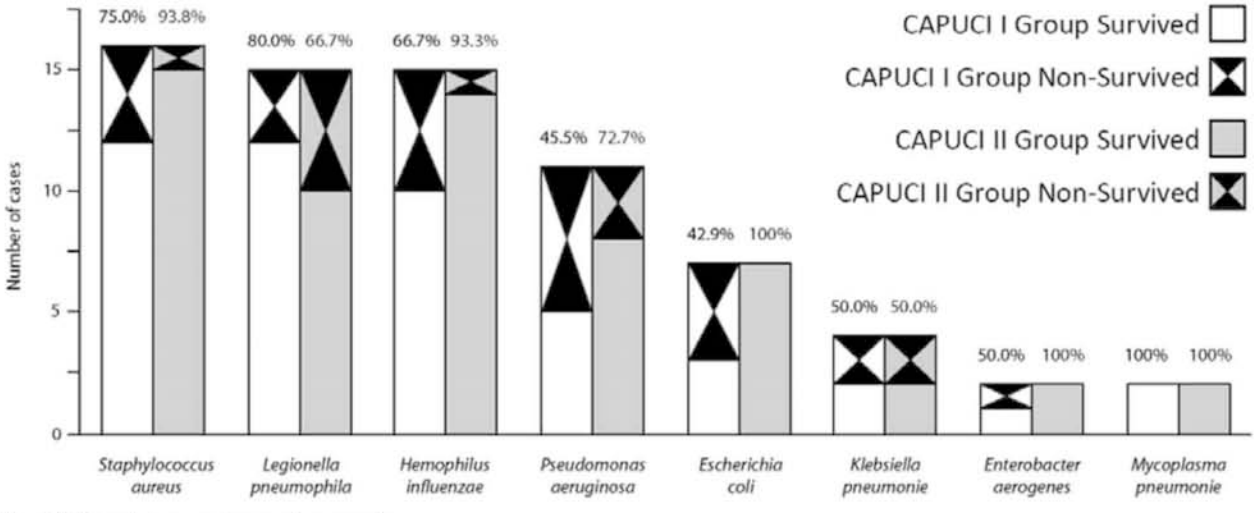

Fig. 2 ICU survival according to microorganism

Table 1 Description of matched variables and mortality

Variable	CAPUCI I group (n = 72)	CAPUCI I non-matched	p value	CAPUCI II group (n = 72)	CAPUCI II non-matched	p value
Age over 65 years	32 (44.4)	22 (28.6)	0.06	32 (44.4)	23 (41.8)	0.86
COPD	34 (47.2)	24 (31.2)	0.06	34 (47.2)	19 (36.5)	0.27
Immunosuppression	9 (12.5)	17 (22.1)	0.14	9 (12.5)	7 (12.5)	1.00
Shock	43 (59.7)	47 (61.0)	1.00	43 (59.7)	24 (43.6)	0.08
IMV	53 (73.6)	57 (74.0)	1.00	53 (73.6)	32 (60.4)	0.13
ICU mortality	25 (34.7)	26 (33.8)	1.00	12 (16.7)	8 (17.4)	1.00

Data are presented as n (%). *COPD* chronic obstructive pulmonary disease, *ICU* intensive care unit, *IMV* invasive mechanical ventilation

while in patients with shock it was 0.60 (95 % CI 0.43–0.84; $p < 0.01$).

Kaplan-Meier survival analysis was performed in the whole population and in the subgroups of patients who underwent IMV or required vasopressors, stratifying by monotherapy versus combined therapy (Fig. 4; log rank p value <0.01 in the three analyses) and early versus non-early antibiotic treatment (Fig. 5; log rank p value <0.01 in all three cases). As shown in Table 3, no significant ldifferences were observed between bacteremic and non-bacteremic patients.

Combined therapy was administered in 76.4 % of patients in the CAPUCI I group and in 90.3 % in the CAPUCI II group (p = 0.04) (Table 4). Early antibiotic treatment was also significantly higher in the CAPUCI II group (63.9 versus 37.5 %; $p < 0.01$). The most frequent antibiotic prescription was a cephalosporin plus a macrolide (Table 5) in 58 out of 144 patients (40.1 %), with ceftriaxone/cefotaxime plus clarithromycin being the most frequent combination (29 patients out of 144, 20.1 %). The most frequent pattern delivered in the CAPUCI I group was ceftriaxone/cefotaxime plus

Table 2 Other demographical data and clinical presentations

Variable	CAPUCI I group (n = 72)	CAPUCI II group (n = 72)	p value
Age[a]	63.0 (47.5–75.0)	62.0 (53.0–72.0)	0.85
Age under 50 years	20 (27.8)	14 (19.4)	0.33
Age 50–64 years	20 (27.8)	24 (33.3)	0.59
Age 65–74 years	13 (18.1)	20 (27.8)	0.23
Age over 75 years	19 (26.4)	14 (19.4)	0.43
Male gender	49 (68.1)	54 (75.0)	0.46
Active smoker	25 (34.7)	27 (37.5)	0.86
Alcohol use	24 (33.3)	14 (19.4)	0.09
Overweight	14 (19.4)	21 (29.2)	0.24
Diabetes mellitus	18 (25.0)	15 (20.8)	0.69
Cardiomyopathy	24 (33.3)	17 (23.6)	0.27
Cerebral vascular disease	4 (5.6)	7 (9.7)	0.53
Malignancy	6 (8.3)	4 (5.6)	0.75
Estimated probability of death[a]	32.0 (19.5–50.0)	34.0 (16.0–62.8)	0.59
ICU length of stay[a]	10.5 (6.0–20.8)	12.0 (7.0–33.0)	0.16
Days of mechanical ventilation[a]	8.0 (4.0–15.3)	10.5 (6.0–23.3)	0.18
Bacteremia	16 (22.2)	22 (30.6)	0.35
Acute kidney injury	31 (43.1)	29 (40.3)	0.87
Rapid radiographic spread	40 (55.6)	37 (51.4)	0.74
ICU mortality	25 (34.7)	12 (16.7)	**0.02**

Data are presented as n (%), unless otherwise indicated: [a] median (interquartile range 25–75). *ICU* intensive care unit. Significant p values are indicated in bold

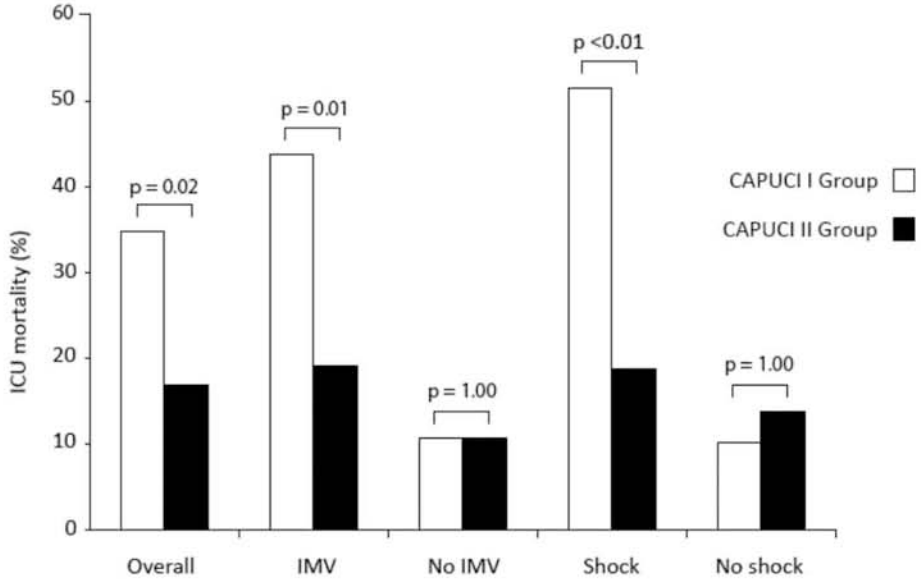

Fig. 3 ICU mortality in the whole population and in different subgroups of patients. *ICU* intensive care unit, *IMV* invasive mechanical ventilation

clarithromycin (27 patients out of 72, 37.5 %) while in the CAPUCI II group it was ceftriaxone/cefotaxime plus levofloxacin (21 patients out of 72, 17.3 %). Azithromycin was not available in Spain in parenteral formulation between 2000 and 2002, so it was not used in this group.

Table 6 shows the empiric antibiotic treatment delivered to each patient, and the appropriateness of the empiric antibiotic treatment with respect to the isolated microorganism. Overall, appropriate therapy based on bacteriology was 91.5 % in CAPUCI I and 92.7 % in CAPUCI II. Appropriate therapy was prescribed in all episodes caused by *Staphylococcus aureus*, *Haemophilus influenzae*, *Escherichia coli*, *Klebsiella pneumoniae*, *Mycoplasma pneumoniae* and *Enterobacter aerogenes*. Inappropriate therapy was only prescribed in episodes caused by *Legionella pneumophila* (2/15 and 2/15 in CAPUCI I and II, respectively) and *Pseudomonas aeruginosa* (6/11 and 5/11 in CAPUCI I and II, respectively).

Table 7 shows univariate and multivariate analyses for the assessment of variables associated with different mortality rates. In the univariate analysis, variables associated with a significant rise in ICU mortality were shock at ICU admission ($p < 0.01$), acute kidney injury ($p < 0.01$), need for IMV ($p = 0.02$) and alcohol use ($p = 0.03$); factors associated with lower ICU mortality were combined therapy ($p < 0.01$) and early antibiotic treatment ($p < 0.01$).

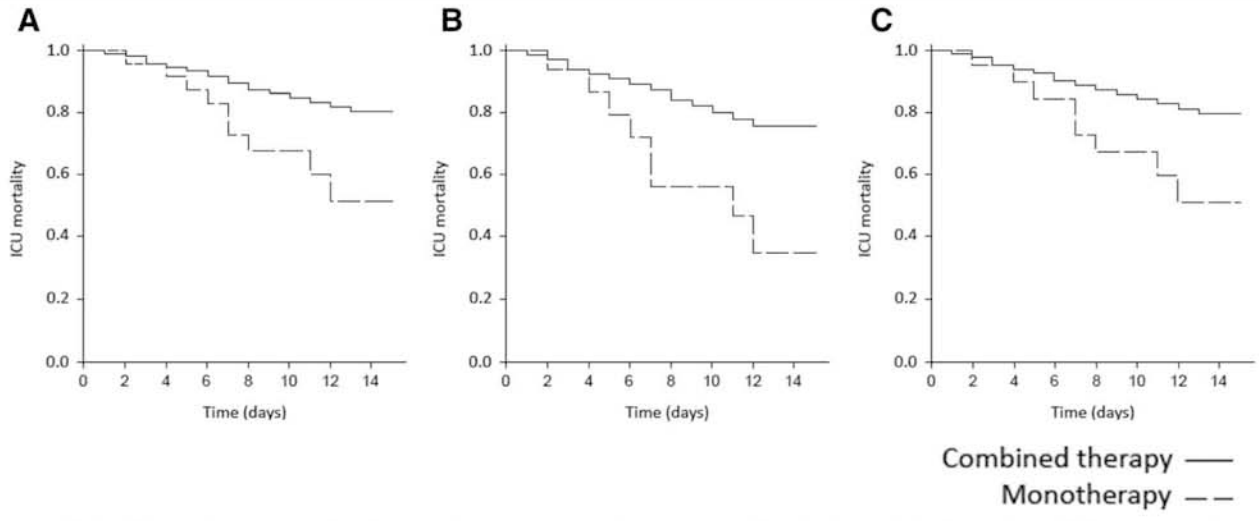

Fig. 4 Kaplan-Meier survival curve stratified for monotherapy versus combined therapy. **a** The whole population (log rank $p < 0.01$); **b** patients with shock (log rank $p < 0.01$); **c** patients under mechanical ventilation (log rank $p < 0.01$). *ICU* intensive care unit

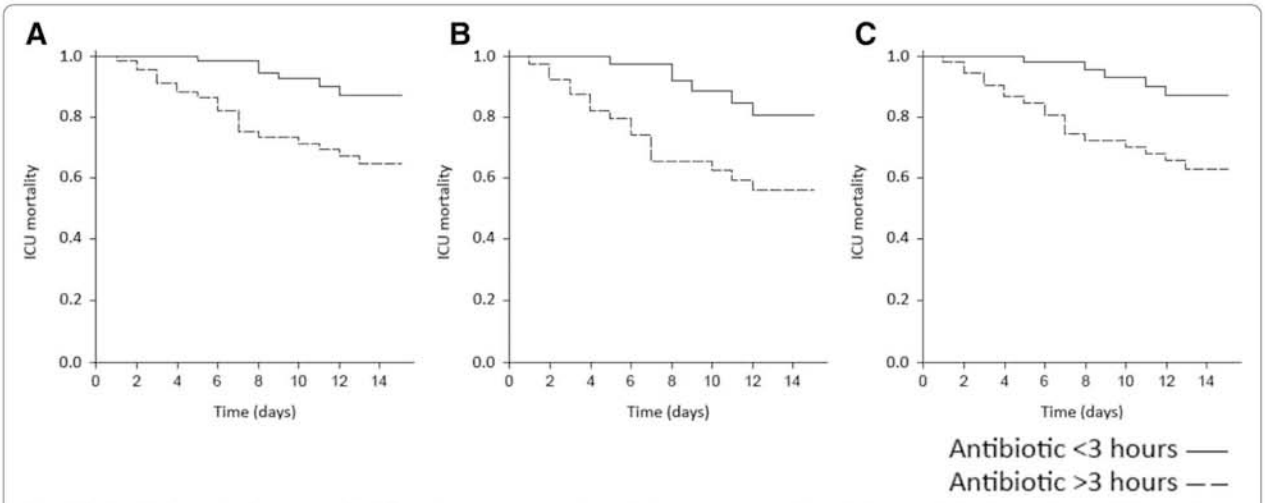

Fig. 5 Kaplan-Meier survival curve stratified for early versus non-early antibiotic treatment. **a** The whole population (log rank $p < 0.01$); **b** patients with shock (log rank $p < 0.01$); **c** patients under mechanical ventilation (log rank $p < 0.01$). *ICU* intensive care unit

As shown in Table 7, we explored whether the administration of a specific antibiotic combination was associated with changes in mortality, without observing significant differences. We compared mortality after the administration of either beta-lactam-macrolide (univariate analysis: OR 0.72, 95 % CI 0.34–1.54) or beta-lactam-quinolone (univariate analysis: OR 0.43, 95 % CI 0.17–1.14) regimens, without observing significant differences (data not shown).

Variables from the univariate analysis that were associated with significant changes in mortality were introduced in a multivariate model analysis. Acute kidney injury and shock at ICU admission were associated with a higher risk of ICU mortality (OR 4.56, 95 % CI 1.60–13.02; and OR 3.96, 95 % CI 1.29–12.14, respectively.

Table 3 Comparison between bacteremic and non-bacteremic patients

Variable	Bacteremic (n = 38)	Non-bacteremic (n = 106)	p value
Age under 50 years	9 (23.7)	25 (23.6)	1.00
Age 50–64 years	13 (34.2)	31 (29.2)	0.68
Age 65–74 years	6 (15.8)	27 (25.5)	0.27
Age over 75 years	10 (26.3)	23 (21.7)	0.65
Immunocompromised	7 (18.4)	11 (10.4)	0.25
Shock at ICU admission	23 (60.5)	63 (59.4)	1.00
Invasive mechanical ventilation	28 (73.7)	78 (73.6)	1.00
Acute kidney injury	17 (44.7)	43 (40.6)	0.70
Rapid radiographic spread	24 (63.2)	53 (50.0)	0.19
Combined therapy	34 (89.5)	86 (81.1)	0.31
Antibiotic initiated 0 to 3 hours	18 (47.4)	55 (51.9)	0.71
ICU mortality	11 (28.9)	26 (24.5)	0.67

Data are presented as n (%). *ICU* intensive care unit

Conversely, early antibiotic treatment (OR 0.07, 95 % CI 0.02–0.22) and combined therapy (OR 0.23, 95 % CI 0.07–0.74) were associated with a lower risk of mortality during ICU admission.

Furthermore, we explored if the agreement with 2007 Infectious Diseases Society of America/American Thoracic Society (IDSA/ATS) guidelines was associated with an improved outcome, observing a decreased mortality after delivery of adequate treatment (OR 0.65, 95 % CI 0.48–0.89). When we performed a multivariate analysis (variable introduced in the model: shock at admission, acute renal failure and 2007 IDSA/ATS agreement) the association was still significantly present (OR 0.39, 95 % CI 0.17–0.91). However, the same association was not present when, in the same multivariate model, the variables "combination therapy" and "early antibiotic administration" were added (for mortality for the variable "2007 IDSA/ATS agreement: OR 0.98; 95 % CI 0.32–2.97).

Discussion

The most relevant conclusions of the present analysis were the significant decrease in ICU mortality due to non-pneumococcal SCAP between the two cohorts, and the positive association between improved empirical antibiotic treatment and a lower mortality rate. These findings confirm our primary hypothesis, and are consistent with the results obtained from our previous study in patients with pneumococcal CAP from the same database [9].

Few published studies have assessed changes in mortality due to CAP in recent years. Moreover, as mentioned above, the vast majority did not differentiate between critical and non-critical patients [3, 4]. However, several studies have reported a significant decrease in mortality due to all-source septic shock in recent

Table 4 Characteristics of antibiotic treatment

Variable	CAPUCI I group (*n* = 72)	CAPUCI II group (*n* = 72)	*p* value
Previous antibiotic	14 (19.4)	10 (13.9)	0.50
Monotherapy	17 (23.6)	7 (9.7)	**0.04**
Combined therapy	55 (76.4)	65 (90.3)	**0.04**
Antibiotic initiated 0 to 3 hours	25 (37.5)	46 (63.9)	**<0.01**
Antibiotic initiated 4 to 6 hours	21 (29.2)	17 (23.6)	0.57
Antibiotic initiated more than 6 hours	25 (33.3)	9 (12.5)	**<0.01**
Adequate according to 2007 IDSA/ATS guidelines	31 (43.1)	41 (56.9)	0.13

Data are presented as n (%). Significant *p* values are indicated in bold. *IDSA/ATS* Infectious Diseases Society of America/American Thoracic Society

decades [5–7]. Our results were obtained in a population with a high rate of IMV (73.6 %) or secondary shock (59.7 %). In this setting, during the planning of a study, we believe that is vital to differentiate between critical and non-critical patients.

To our knowledge, no studies to date have assessed mortality due to SCAP with regard to etiology. It is worth noting that, during the matching process, we did not set a percentage for each microorganism a priori; instead, we found the number of coincidences between groups according to the above-mentioned variables. Interestingly, the distribution of the identified microorganisms in our sample coincides with literature reports, thus confirming the study's external reproducibility [1, 17].

As indicated in Table 6, the vast majority of patients received adequate treatment according to microbiology. As expected, appropriateness of treatment in case of infection due to *Legionella pneumophila* and *Pseudomonas aeruginosa* was lower. In case of *Legionella* infection the treatment was adequate in 86.7 % of patients from the CAPUCI I and II groups. On the other hand, treatment was adequate with respect to microbiology respectively in 45.5 and 54.5 % of patients with infection due to *Pseudomonas aeruginosa*. This is important because an inappropriate treatment can lead to an increased mortality. In fact, the survival rate in case of *Pseudomonas* pneumonia was the lowest when compared with other etiologies (with the exception of *Enterobacter* infection; however, this is not significant as only four patients were introduced in the analysis, two in each group), and this is probably due to the low rate of adequate empirical treatment. Despite this, an improvement in mortality was observed between the two periods, and this is probably due to the earlier administration of the first dose of antibiotic and other general

Table 5 Most frequent patterns of antibiotic treatment

Variable	All patients (*n* = 144)	CAPUCI I group (*n* = 72)	CAPUCI II group (*n* = 72)	*p* value
Cephalosporin and macrolide	58 (40.1)	35 (48.5)	23 (32.0)	0.06
Ceftriaxone/cefotaxime and clarithromycin	29 (20.1)	27 (37.5)	2 (2.8)	**<0.01**
Ceftriaxone/cefotaxime and azithromycin	18 (12.4)	0 (0)	18 (25.0)	**<0.01**
Other cephalosporin and macrolide	11 (7.6)	8 (11.1)	3 (4.2)	0.21
Cephalosporin and quinolone	31 (21.5)	6 (8.4)	25 (34.6)	**<0.01**
Cefotaxime/ceftriaxone and levofloxacin	25 (17.3)	4 (5.6)	21 (29.0)	**<0.01**
Other cephalosporin and quinolone	6 (4.2)	2 (2.8)	4 (5.6)	0.68
Penicillin and macrolide	9 (6.3)	2 (2.8)	7 (9.7)	0.17
Piperacillin-tazobactam and azithromycin	5 (3.5)	0 (0)	5 (6.9)	0.06
Other penicillin and macrolide	4 (2.8)	2 (2.8)	2 (2.8)	1.00
Amoxicillin-clavulanate	8 (5.6)	8 (11.1)	0 (0)	**<0.01**
Ceftriaxone/cefotaxime	7 (4.9)	5 (6.9)	2 (2.8)	0.44
Levofloxacin	6 (4.2)	4 (5.6)	2 (2.8)	0.68
Miscellaneous combined therapy	22 (15.3)	12 (16.7)	10 (13.9)	0.78
Miscellaneous monotherapy	3 (2.1)	0 (0)	3 (4.2)	0.25
Overall	144 (100)	72 (100)	72 (100)	

Data are presented as n (%). Significant *p* values are indicated in bold. *p* value calculated between CAPUCI I and CAPUCI II groups

Table 6 Treatment of each case of pneumonia and rate of adequate treatment according with the isolated microorganism

	Staphylococcus aureus		*Legionella pneumophila*		*Haemophilus influenzae*		*Pseudomonas aeruginosa*		*Escherichia coli*		*Klebsiella pneumoniae*		*Mycoplasma pneumoniae*		*Enterobacter aerogenes*	
	C I	C II	C I	C II	C I	C II	C I	C II	C I	C II	C I	C II	C I	C II	C I	C II
Amoxicillin-clavulanate	1 (0)	–	1 (1)	–	5 (3)	–	1 (1)	–	–	–	–	–	–	–	–	–
Cefotaxime/ceftriaxone	3 (1)	–	1 (0)	2 (2)	–	–	–	–	–	–	–	–	–	–	1 (1)	–
Levofloxacin	1 (0)	–	–	–	–	1 (0)	1 (1)	1 (1)	2 (1)	–	–	–	–	–	–	–
Piperacillin-tazobactam	–	1 (0)	–	–	–	–	–	1 (1)	–	1 (0)	–	–	–	–	–	–
Amoxicillin-clavulanate plus macrolide	–	–	1 (0)	1 (1)	–	–	–	–	–	–	–	–	–	–	–	–
Amoxicillin-clavulanate plus clindamycin	–	–	–	–	–	–	–	–	–	1 (0)	–	–	–	–	–	1 (0)
Amoxicillin-clavulanate plus levofloxacin	–	1 (0)	–	–	–	–	–	–	–	–	–	1 (1)	–	–	–	–
Cefotaxime/ceftriaxone plus macrolide	9 (2)	7 (0)	6 (0)	5 (2)	5 (2)	3 (0)	4 (2)	2 (0)	1 (1)	2 (0)	3 (1)	–	1 (0)	1 (0)	–	–
Cefotaxime/ceftriaxone plus aztreonam	–	–	–	–	–	–	1 (0)	–	–	–	–	–	–	–	–	–
Cefotaxime/ceftriaxone plus clindamycin	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Cefotaxime/ceftriaxone plus levofloxacin	1 (1)	2 (0)	1 (1)	5 (0)	–	6 (0)	–	2 (0)	1 (0)	3 (0)	1 (1)	1 (0)	–	1 (0)	–	1 (0)
Cefepime/ceftazidime plus macrolide	–	1 (0)	1 (0)	1 (0)	3 (0)	1 (0)	1 (1)	–	1 (1)	–	–	–	–	–	–	–
Cefepime plus amikacin	–	–	–	–	–	–	–	–	1 (1)	–	–	–	–	–	–	–
Cefepime plus ciprofloxacin	–	–	1 (0)	–	1 (0)	–	–	–	–	–	–	–	–	–	–	–
Cefepime plus levofloxacin	–	2 (1)	–	–	–	2 (0)	–	–	–	–	–	–	–	–	–	–
Carbapenem/piperacillin-tazobactam plus amikacin	–	–	–	–	–	–	1 (0)	–	–	–	–	–	–	–	–	–
Carbapenem/piperacillin-tazobactam plus clindamycin	–	1 (0)	–	–	1 (0)	–	–	–	–	–	–	–	–	–	–	–
Carbapenem/piperacillin-tazobactam plus ciprofloxacin	1 (0)	–	–	–	–	–	2 (1)	–	–	–	–	–	1 (0)	–	–	–
Carbapenem/piperacillin-tazobactam plus macrolide	–	1 (0)	1 (1)	–	–	1 (1)	–	4 (1)	–	–	–	–	–	–	1 (0)	–
Levofloxacin plus azithromycin	–	–	–	1 (0)	–	1 (0)	–	–	–	–	–	–	–	–	–	–
Levofloxacin plus tobramycin	–	–	–	–	–	–	–	–	1 (0)	–	–	–	–	–	–	–
Piperacillin-tazobactam plus levofloxacin	–	–	2 (0)	–	–	–	–	1 (0)	–	–	–	2 (1)	–	–	–	–
Overall	16	16	15	15	15	15	11	11	7	7	4	4	2	2	2	2
Adequate according with microorganism[a]	16 (100)	16 (100)	13 (86.7)	13 (86.7)	15 (100)	15 (100)	5 (45.5)	6 (54.5)	7 (100)	7 (100)	4 (100)	4 (100)	2 (100)	2 (100)	2 (100)	2 (100)

Data are shown as absolute count of patients that received a specific antibiotic regimen; the number of patients who died receiving this antibiotic regimen is shown between parenthesis. [a] Data are presented as *n* (%). *C I* CAPUCI I, *C II* CAPUCI II

Table 7 Univariate and multivariate analyses to assess variables associated with changes in ICU mortality

Variable	Survival (n = 107)	No survival (n = 37)	Univariate analysis p value	Multivariate analysis: OR (95 % CI); p value
Age over 65 years	46 (43.0)	18 (48.6)	0.57	
Overweight	27 (25.2)	8 (21.6)	0.83	
Alcohol use	23 (21.5)	15 (40.5)	**0.03**	
Active smoker	36 (33.6)	16 (43.2)	0.33	
Diabetes mellitus	24 (22.4)	9 (24.3)	0.83	
Cardiomyopathy	28 (26.2)	13 (35.1)	0.30	
COPD	49 (45.8)	19 (51.4)	0.57	
Immunosuppression	13 (12.1)	5 (13.5)	0.78	
Shock at ICU admission	56 (52.3)	30 (81.1)	**<0.01**	3.96 (1.29–12.14); **0.02**
Invasive mechanical ventilation	73 (68.2)	33 (89.2)	**0.02**	
Acute kidney injury	36 (33.6)	24 (64.9)	**<0.01**	4.56 (1.60–13.02); **<0.01**
Rapid radiographic spread	56 (52.3)	21 (56.8)	0.70	
Bacteremia	27 (25.2)	11 (29.7)	0.67	
Combined therapy	96 (89.7)	24 (64.9)	**<0.01**	0.23 (0.07–0.74); **0.01**
AB initiated within 3 hours	67 (62.6)	6 (16.2)	**<0.01**	0.07 (0.02–0.22); **<0.01**
Combined BL and M therapy	52 (48.6)	15 (40.5)	0.45	
Combined BL and FQ therapy	33 (30.8)	6 (16.2)	0.09	

Data are presented as n (%). Significant p values are indicated in bold. *AB* antibiotic, *BL* beta-lactam, *CI* confidence interval, *COPD* chronic obstructive pulmonary disease, *FQ* fluoroquinolone, *ICU* intensive care unit, *M* macrolide, *OR* odds ratio

improvements that have been made in the last years in the management of ICU patients.

When exploring mortality depending on the etiology of pneumonia, we observed an increased survival between the two cohorts when pneumonia was caused by *Staphylococcus aureus*, *Haemophilus influenzae*, *Pseudomonas aeruginosa*, *Escherichia coli* and *Enterobacter aerogenes*. No changes were observed in case of *Klebsiella* infection, and an increased mortality was observed in case of *Legionella* pneumonia. As shown in Table 3, a higher proportion of patients from CAPUCI II received early combination therapy. When exploring the administration of mono- versus combination therapy, differentiating by the microorganisms, it becomes evident that all cases with the exception of *Legionella* and *Pseudomonas* infections received a higher rate of combined therapy if belonging to the CAPUCI II group (Table 6). Thus, it is reasonable to assume that the decrease in mortality in our sample was mainly caused by a higher rate of combination therapy and early antibiotic administration.

In the case of pneumonia due to *Legionella pneumophila*, an increased mortality between the two groups was observed. Fifteen patients with *Legionella* infection were included in both groups: 3 out of 15 and 5 out 15 died, respectively, in the CAPUCI I and II groups. Among those who died, two individuals out of three from the CAPUCI I cohort received microbiological adequate coverture (one received a quinolone regimen while the other a macrolide regimen); in CAPUCI II, they were three out of five (all received a macrolide regimen) (Table 6). On the other hand, all patients but one (belonging to the CAPUCI II group) received delayed antibiotic treatment. We assume that the small size of the sample, fortuity and probably some unrecognized factor other than antibiotic therapy played a role in the different mortality. Due to the low number of patients that died because of *Legionella* infection, it is difficult to ascribe changes in mortality because of the use of quinolones rather than macrolides, although it is not possible to exclude it.

In the case of *Klebsiella* infection, due to the reduced number of cases (four patients for each group, with 50 % mortality in both cohorts), it is not possible to take definitive conclusions.

Another important finding is the association between lower mortality and an improvement in antibiotic strategies; that is, combined antibiotic therapy and early treatment initiation. Combined therapy has become common practice in the empirical treatment of SCAP [1]. To our knowledge, no current guideline suggests monotherapy as empirical therapy. Generally, the recommendation is a beta-lactam plus either a macrolide or a quinolone. In the CAPUCI I group, monotherapy was administered in 17 patients (23.6 %) and in 7 patients (9.7 %) in the CAPUCI II group.

Univariate and multivariate analysis, and Kaplan-Meier survival analysis, all showed a positive association between

delivery of combined antibiotic therapy and lower mortality. Previous studies observed that patients with CAP and secondary shock or bacteremia [18, 19] presented lower mortality when combined therapy was delivered. Our results confirm these findings and, furthermore, suggest that all patients with severe pneumonia, with or without shock or need for IMV, may benefit from combined therapy. Even though this may not be a surprising conclusion, it should be noted that a significant percentage of our population and those in other studies still received monotherapy [20]. These findings are consistent with those reported in patients with pneumococcal SCAP [9].

To date, the optimal antibiotic combination choice in severe CAP is still a debated issue; some authors advocate the use of a macrolide-regimen administration, due to the anti-inflammatory effects shown by these molecules [21]. However, not all studies achieved similar results. Although in our cohort the limited size of the sample makes it difficult to explore this issue, we assessed changes in mortality after macrolide or quinolone administration, in the whole population (Table 7) and in the subgroups of patients with shock or under mechanical ventilation (data not shown)—no differences were observed. Furthermore, several studies concluded that quinolone administration is comparable in terms of mortality with a macrolide regimen, but with a higher eradication rate, a lower treatment failure and possibly less cost of treatment [22]; however, concerns about an increased resistance rate after quinolone administration were raised [23]. Moreover, in case of a social environment with high rates of pulmonary tuberculosis, the use of a fluoroquinolone could mask a pulmonary tuberculosis rather than bacterial CAP [24]. In our sample, the use of a quinolone regimen showed a trend to lower mortality, without achieving significant results, in the whole population and in the subgroups of patients with shock or under mechanical ventilation. According to the present results, it is not possible to advocate the use of a specific antibiotic family.

In 2006, Kumar et al. showed that mortality rates in septic patients with shock increased in line with the delay in antibiotic initiation [25]. Subsequent other studies of patients with shock confirmed this finding [26]. As shown in the Kaplan-Meier survival analysis (Fig. 5), early antibiotic treatment in our sample was associated with lower mortality not only in the subgroup of patients with shock, but in the overall population and in the subgroup of ventilated patients as well. In view of these findings, each patient who presents at the emergency room with non-pneumococcal SCAP should receive the first dose of antibiotic treatment within the first 3 hours. Indeed, the 2007 IDSA/ATS guidelines recommend initiation of antibiotic therapy before transfer to the ward or to the ICU [1].

We explored if the agreement with the 2007 IDSA/ATS guidelines was associated with different outcomes, and we found a reduced mortality when guideline recommendations were followed. Basically, IDSA/ATS guidelines recommend the administration of an early combination of specific antibiotic families; thus, to better investigate the effects of simple medical actions on mortality, we decided to separate the item "2007 IDSA/ATS adequate treatment" into two variables: "combined therapy" and "early antibiotic treatment". Thus, after the addition of these two variables in the multivariate model this association was no longer documented. This might suggest that the sum of actions that imply the agreement to international guidelines is better investigated by separating these actions in multiple variables rather that grouping all actions into the variable "2007 IDSA/ATS adequate treatment".

The current study has some limitations that should be mentioned. The most important is its observational nature; however, this approach is the only way to assess changes in outcome over a period of time. Moreover, in the ICU setting in recent decades there have been significant improvements in the management of patients undergoing IMV or resuscitation of septic shock, and in nutrition, in the prevention of ICU-related complications and in the ICU admission criteria as well. Severity-of-illness was recorded with different scores; in CAPUCI I the risk of mortality was estimated using APACHE II score while in CAPUCI II SAPS III was used. However, both scales reflect a reliable risk of death and were widely validated in large-scale studies. For this, after estimating the risk of death with APACHE II and SAPS III scores, we created a variable named "estimated probability of death", comparing both groups. Furthermore, to avoid an overlap between the same parameters in different variables, we decided not to use severity-score variables to match patients; in fact, both APACHE II and SAPS III scores include parameters of severity for respiratory or cardiac failure, and demographics such as age, which were introduced independently in the matching. Of note, the ICUs that participated in CAPUCI I and II studies were different; in fact, CAPUCI I was developed in 33 Spanish ICUs while CAPUCI II was carried out in 29 ICUs–24 from Spain and 5 from other European countries. This may originate a bias due to a different source of patients; however, after the matching process, we retrospectively observed that all 72 patients from the CAPUCI II cohort were enrolled from Spanish ICUs, thus minimizing the risk of a significant bias. Moreover, we did not perform genetic investigations, although recent publications have identified common variants in specific genes that are associated with different outcomes in severe pneumonia [27]. Finally, as stated by Waterer [28], ICU outcome often differs from hospital outcome or from outcome on day 60 or 90 after admission. However,

as shown in the Kaplan-Meier survival analysis, the majority of deaths in our sample occurred within 14 days of admission. Although it is true that ICU mortality may differ from hospital or 3-month outcome, we feel that deferring excessively the time of the study of the outcome may complicate the analysis, because more variables that are difficult to record and interpret have to be introduced in the analysis as confounding variables.

Conclusions

In the current study, mortality due to non-pneumococcal SCAP decreased between the two cohorts, and the use of combined antibiotic therapy and early antibiotic administration were associated with lower mortality. These finding agree with the conclusions obtained in a previous study carried out in patients with pneumococcal SCAP from the same database [9]. More studies to confirm these findings are now needed. In the meantime, all patients presenting at the emergency department with SCAP should receive two antibiotics within 3 hours of admission.

Key messages

- In the last 14 years, a significant reduction in ICU mortality due to severe community-acquired pneumonia was observed.
- In severe non-pneumococcal community-acquired pneumonia, early antibiotic administration and combination therapy were associated with a significant improved survival.
- A lower mortality was observed following early administration of combination therapy either in the subgroups of patients with shock, under mechanical ventilation and without shock or requirement of mechanical ventilation.
- The most frequent etiologies in severe CAP in the present cohort were *Staphylococcus aureus* followed by *Legionella pneumophila* and *Haemophilus influenzae*.

Abbreviations

APACHE: Acute Physiology and Chronic Health Evaluation; CAP: Community-acquired pneumonia; CI: Confidence interval; ICU: Intensive care unit; IDSA/ATS: Infectious Diseases Society of America/American Thoracic Society; IMV: Invasive mechanical ventilation; OR: Odds ratio; SAPS: Simplified Acute Physiology Score; SCAP: Severe community-acquired pneumonia.

Competing interest

JR serves on the speaker's bureau and advisory boards for Pfizer and Aridis. RZ serves on the speaker's bureau and advisory boards for Pfizer. The other authors declare that they have no competing interests.

Authors' contributions

SG is the guarantor of the manuscript and takes responsibility for the content of the paper, including the data and analysis. SG and JR conceived, designed and drafted the manuscript. LL, LV, JS-V, RZ, JV, AT, RSi and RSe made substantial contribution to the interpretation of the data and the final revision of the manuscript, and have provided final approval of the version to be published. All authors read and approved the final manuscript.

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VI. DISCUSIÓN

DISCUSIÓN

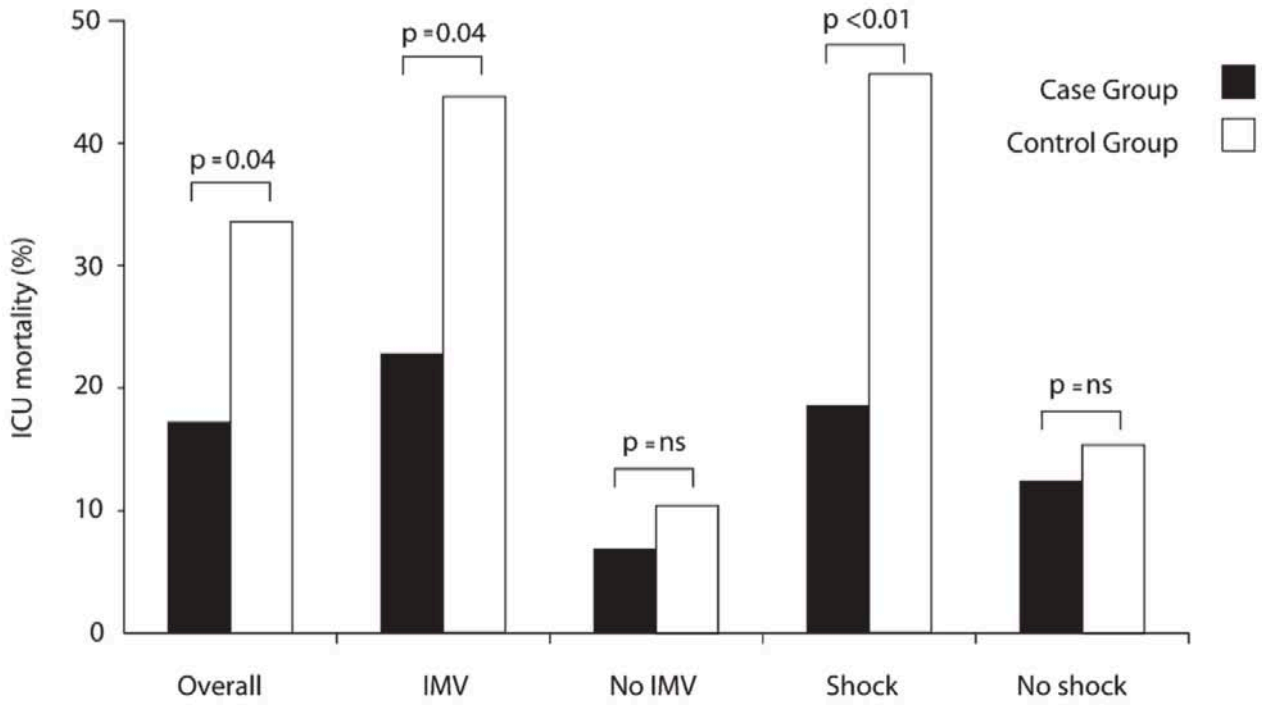
Primer artículo original de la tesis: Estudio caso-control que evalúa cambios de mortalidad tras la administración de uno o dos antibióticos y de antibioticoterapia precoz o tardía, en una muestra de pacientes con neumonía grave neumocócica.

El resultado más importante del primer estudio fue la disminución de la mortalidad de un 15% en pacientes con NACG causado por *Streptococcus pneumoniae*, entre los dos períodos a estudio. Así mismo, se documentó una asociación entre disminución de la mortalidad y administración de tratamiento antibiótico combinado y disminución de la mortalidad y administración precoz de la primera dosis de antibiótico.

Según datos de la Organización Mundial de la Sanidad, la mortalidad por neumonía en los últimos años presentó una mínima y no significativa disminución: 4.1 millones en 1993 frente a 3.9 millones en 2002 (106,107). Según otros estudios, en las últimas décadas la mortalidad secundaria a infección de cualquier foco habría aumentado, en Estados Unidos, hasta un 58% (108,109). Sin embargo, interpretar estos datos es complicado y puede llevar a malentendidos, ya que no se hizo diferenciación según la gravedad de la infección: infección local, sepsis, sepsis grave y shock séptico. En este contexto, es importante destacar algo ya ampliamente conocido: la infección local de cualquier órgano o tejido se asocia a una fisiopatología diferente que la infección complicada con sepsis o shock séptico (110). Además, en la mayoría de los estudios publicados no hay datos sobre el porcentaje de pacientes candidatos a curas paliativas o de aquellos pacientes en que la infección se consideró como un evento terminal en un paciente con elevada comorbilidad decidiéndose iniciar únicamente medidas de confort.

Por otro lado, varios artículos observaron una disminución de mortalidad por sepsis grave y shock séptico en los últimos años (111,112): un estudio publicado por Lagu et al. documentó una disminución global de hasta un 12%, en pacientes con sepsis grave y shock séptico de cualquier origen (113). Posibles explicaciones de esta tendencia podrían individualizarse en una mayor adherencia a las recomendaciones internacionales (114,115), un mejor empleo de los recursos farmacológicos (89,116,117), un mejor manejo de la resucitación del shock séptico (88), un uso más generalizado de ventilación mecánica protectora (118,119) y finalmente una mayor tasa de pacientes no ingresados en UCI por orden de no RCP por presencia de comorbilidades o por presentar un pronóstico muy desfavorable (113). En la figura 3 se muestra la tasa de mortalidad en toda la cohorte y en los subgrupos con shock y conectados a VMI.

Figura 3: mortalidad en toda la cohorte y en los subgrupos de pacientes con shock y VMI.



Los resultados del presente análisis muestran una asociación entre tratamiento antibiótico combinado y disminución de la mortalidad, en línea con los resultados obtenidos en otros estudios (120-123); sin embargo, la totalidad de estos estudios incluía únicamente pacientes con neumonía y shock secundario. Nuestros resultados muestran una mayor supervivencia en los pacientes que reciben tratamiento combinado en toda la población a estudio, en el subgrupo de pacientes con shock y de pacientes conectados a VMI; este resultado sugiere como el tratamiento combinado podría beneficiar todos los pacientes ingresados en UCI, y no solo los pacientes con neumonía y shock.

Pese a los estudios disponibles, todavía no esta clara la razón del beneficio de la terapia antibiótica combinada; posibles explicaciones son: cobertura frente a microorganismos atípicos, más probabilidad de cubrir bacterias resistentes a antibióticos, efecto sinérgico de los dos antibióticos, el efecto antiinflamatorio propio de algunas familias antibióticas (123). En el presente estudio, ya que todos los casos eran de etiología neumocócica, es razonable asumir que la disminución de la mortalidad no es debida a la cobertura de otros microorganismos o a las resistencias bacterianas.

Otra conclusión obtenida en el presente análisis es la asociación entre reducción de la mortalidad y administración precoz de la primera dosis de antibiótico. En general, los estudios anteriores que no encontraron diferencias en mortalidad tras la administración precoz de la primera dosis de antibiótico no diferenciaban entre paciente critico y no critico (124,125).

Por otro lado, se ha demostrado ampliamente como la administración precoz de antibiótico se asocia a una reducción de la mortalidad en

pacientes con sepsis grave o shock séptico, independientemente del origen de la infección (89,116,117). La actualización de 2012 de la Surviving Sepsis Campaign recomienda en este sentido administrar la primera dosis de antibiótico lo antes posible, idealmente en la primera hora tras el diagnóstico (88).

En el presente artículo se documentó una disminución significativa de la mortalidad en pacientes con neumonía grave neumocócica que recibieron tratamiento antibiótico combinado de forma precoz; a la luz de los presentes resultados, cada paciente que acude a urgencias y que se diagnostica de neumonía comunitaria grave neumocócica debería recibir dos antibióticos de forma precoz. En las figuras 4 y 5 se muestran las curvas de supervivencia Kaplan-Meier en toda la cohorte y en los subgrupos de pacientes con shock y conectados a VMI, tras estratificación entre recibir uno o dos antibióticos y antibioticoterapia precoz y tardía.

Figura 4: supervivencia en toda la cohorte y en los pacientes con shock y VMI, tras estratificar por tratamiento combinado o monoterapia.

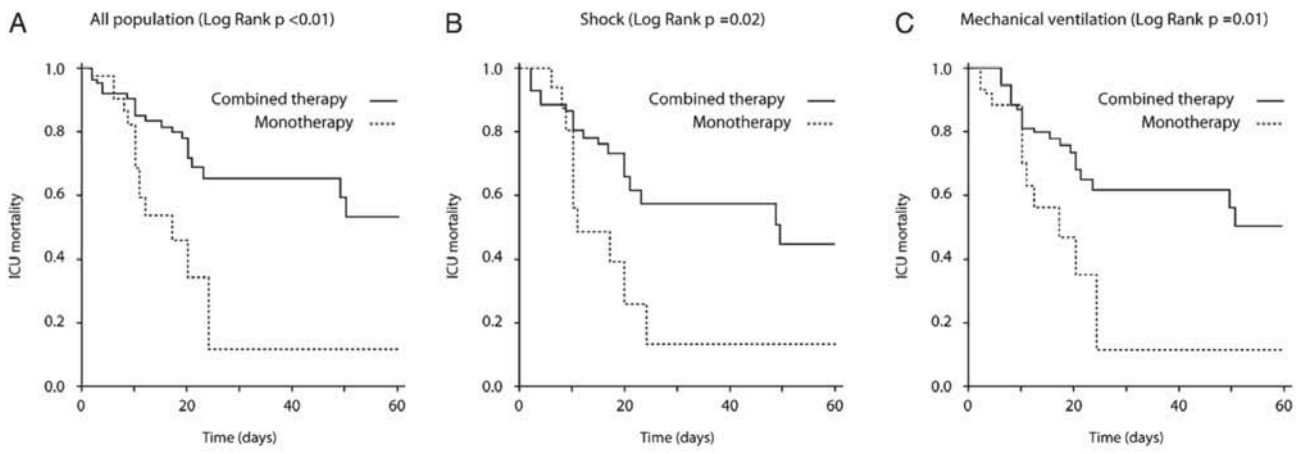
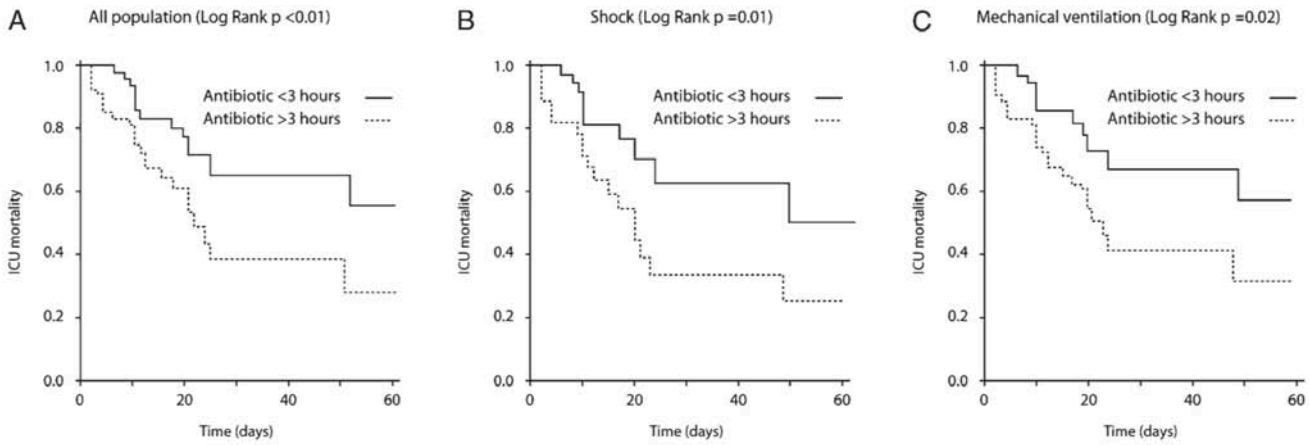


Figura 5: supervivencia en toda la cohorte y en los pacientes con shock y VMI, tras estratificar por antibioticoterapia precoz versus tardía.



Las pautas antibióticas administradas en los dos grupos presentan diferencia significativas; la más importante es que durante el período de estudio del CAPUCI I no se administró azitromicina, un potente macrólido. Esto es debido a que en los años de realización del estudio CAPUCI I la formulación parenteral de azitromicina no estaba disponible. Además, en el grupo CAPUCI I se usó de forma más generalizada antibioticoterapia de amplio espectro; se usaron más familias de antibióticos y la adherencia a las recomendaciones fue menos frecuente (80.0% versus 47.6%). Se analizó si diferentes pautas antibióticas se asociaban a mortalidad diferente, sin encontrar diferencias significativas.

En resumen la mortalidad por neumonía neumocócica grave disminuyó en los últimos años de hasta un 15%; el aumento de la supervivencia se asoció a un uso más generalizado de tratamiento antibiótico combinado y la administración precoz de la primera dosis de antibiótico. Otros estudios previamente analizaron esta asociación, pero el presente es el primer estudio que analiza estas asociaciones en una muestra homogénea de pacientes críticos, sin analizar únicamente pacientes con

shock séptico.

Segundo artículo original de la tesis: Estudio caso-control que evalúa cambios de mortalidad tras la administración de uno o dos antibióticos y de antibioticoterapia precoz o tardía, en una muestra de pacientes con neumonía grave bacteriana no neumocócica.

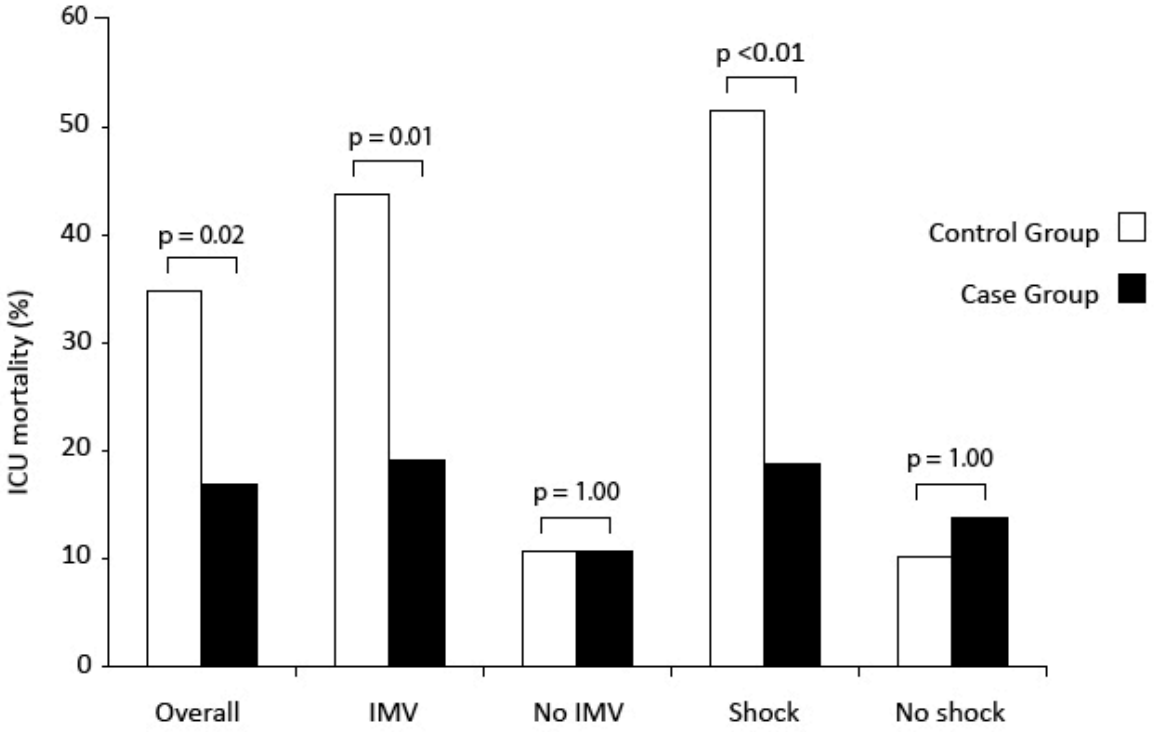
El segundo estudio realizado tenía como finalidad investigar los mismos objetivos que el primero, pero en una población diferente. Se buscaron eventuales diferencias de mortalidad entre los dos grupos de pacientes con neumonía comunitaria grave bacteriana no neumocócica, y si la administración de dos antibióticos de forma precoz se asociaba a diferente mortalidad.

El resultado más significativo fue una disminución del 18% de la mortalidad en UCI entre los dos períodos a estudio, además de confirmar una asociación positiva entre la administración precoz de dos antibióticos y reducción de la mortalidad en UCI.

Revisando la literatura, no se encontraron estudios que analicen la evolución de la mortalidad en la neumonía comunitaria grave bacteriana no neumocócica. Además, al igual que en casos de estudios sobre pacientes con neumonía neumocócica, no se diferencia entre neumonía leve, moderada o grave. Esto es importante porque la proporción de pacientes con neumonía moderada o grave puede ser diferente en los diferentes estudios, y los desenlaces clínicos varían de forma significativa entre casos de neumonía leve, moderada o grave (36). El estudio que llevamos a cabo incluye únicamente casos de neumonía grave, con una alta incidencia de shock séptico (59.7%) o necesidad de ventilación mecánica (73.6%), garantizando una suficiente homogeneidad de la

muestra con respecto a otras muestras de pacientes críticos. La figura 6 indica la mortalidad en toda la cohorte y en los subgrupos de pacientes con shock o conectados a VMI.

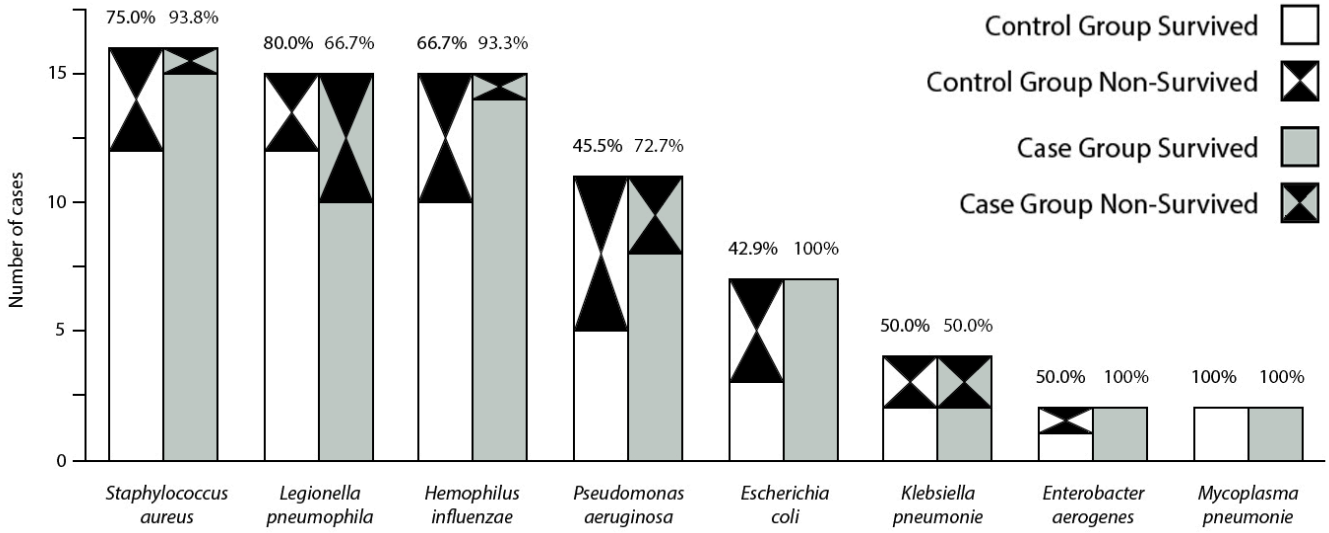
Figura 6: mortalidad en toda la cohorte y en los subgrupos de pacientes con shock y VMI.



Tras una búsqueda exhaustiva en la literatura, no encontramos estudios que exploren los desenlaces clínicos en pacientes con neumonía grave, dependiendo de la etiología. Es relevante destacar como durante el apareamiento entre los grupos CAPUCI I y II no establecimos a priori un número específico de pacientes en función de la etiología. Lo que se hizo fue identificar y comparar las variables establecidas para el apareamiento, e introducir en los grupos de los casos y controles solo los

pacientes con una coincidencia de la totalidad de las variables a estudio. Notablemente, la distribución de las etiologías halladas en los dos grupos tiene la misma distribución de las etiologías reportadas en la literatura, confirmando la reproducibilidad externa de la selección de la muestra de los grupo de casos y controles, con respeto a los grupos de las bases de datos CAPUCI I y II (36,126). En la figura 7 se indica la mortalidad en función de la microbiología.

Figura 7: mortalidad en toda la cohorte dependiendo de la etiología.



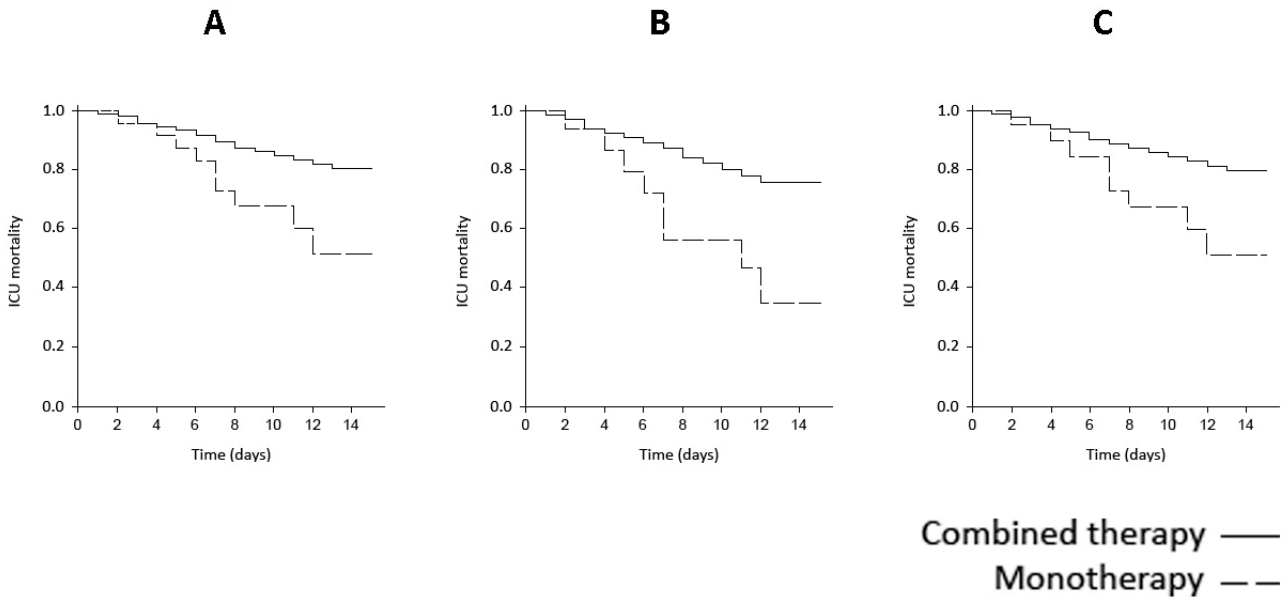
Tras confrontar la mortalidad dependiendo de la etiología de la neumonía se observó aumento de la supervivencia entre las dos temporadas en caso de infección por *Staphylococcus aureus*, *Haemophilus influenzae*, *Pseudomonas aeruginosa, Escherichia coli* y *Enterobacter aerogenes*. No se observaron cambios en caso de infección por *Klebsiella pneumoniae* y se documento aumento de mortalidad en caso de neumonía por *Legionella pneumophila*. Como regla general es

razonable plantear la hipótesis que en nuestra muestra la reducción de la mortalidad sea debida a un mayor uso de antibioticoterapia empírica combinada y precoz. En el caso de neumonía por *Klebsiella*, debido al número reducido de casos (4 casos por grupo, con un 50% de mortalidad en ambos grupos), no es posible sacar conclusiones definitivas. Finalmente, en el caso de neumonía por *Legionella pneumophila*, se observó un aumento de la mortalidad entre los dos grupos. En ambos grupos hubo un total de 15 pacientes con neumonía por *Legionella*: 3 de 15 y 5 de 15 fallecieron respectivamente en los grupos CAPUCI I y II. De los pacientes fallecidos, 2 individuos sobre 3 del grupo CAPUCI I recibieron un tratamiento adecuado (un paciente recibió una pauta con betalactámico y quinolona mientras que el otro recibió una pauta con betalactámico y macrólido); por otro lado, en el grupo CAPUCI II, 3 pacientes fallecidos sobre 5 recibieron un tratamiento adecuado (todos recibieron una pauta con betalactámico y un macrólido). Por otro lado, todos los pacientes excepto uno, perteneciente al grupo CAPUCI II, recibieron tratamiento no precoz. Debido al reducido número de pacientes, consideramos que no es posible sacar conclusiones ante los resultados obtenidos, posiblemente el caso, o algún otro factor no dependiente de la antibioticoterapia sea responsable del cambio de mortalidad. Las diferentes pautas de antibióticos que recibieron los pacientes podría contribuir al cambio de mortalidad, pero otra vez debido al reducido número de pacientes fallecidos no es posible sacar conclusiones definitivas. En un estudio publicado por nuestro grupo de investigación se observó disminución de mortalidad en pacientes con *Legionella pneumophila* y shock séptico que recibían tratamiento antibiótico combinado (127).

Otro resultado significativo es la asociación entre disminución de mortalidad y la optimización de tratamiento antibiótico, o sea la administración de antibioticoterapia combinada y la administración precoz de la primera dosis de antibiótico.

El tratamiento antibiótico combinado es una práctica común en el tratamiento empírico de la NACG (36), según nuestros conocimientos no hay ninguna recomendación internacional que recomienda monoterapia en la NACG. En general, la recomendación es de administrar un betalactámico asociado a un macrólido o una quinolona. En el grupo CAPUCI I se administró monoterapia en 17 pacientes (23.6%) y en 7 pacientes (9.7%) en el grupo CAPUCI II.

Figura 8: supervivencia en toda la cohorte y en los pacientes con shock y VMI, tras estratificar por tratamiento combinado o monoterapia.



Los análisis univariante, multivariante y las curvas de supervivencia Kaplan-Meier (figura 8) confirmaron la asociación entre administración de tratamiento antibiótico combinado y reducción de la mortalidad.

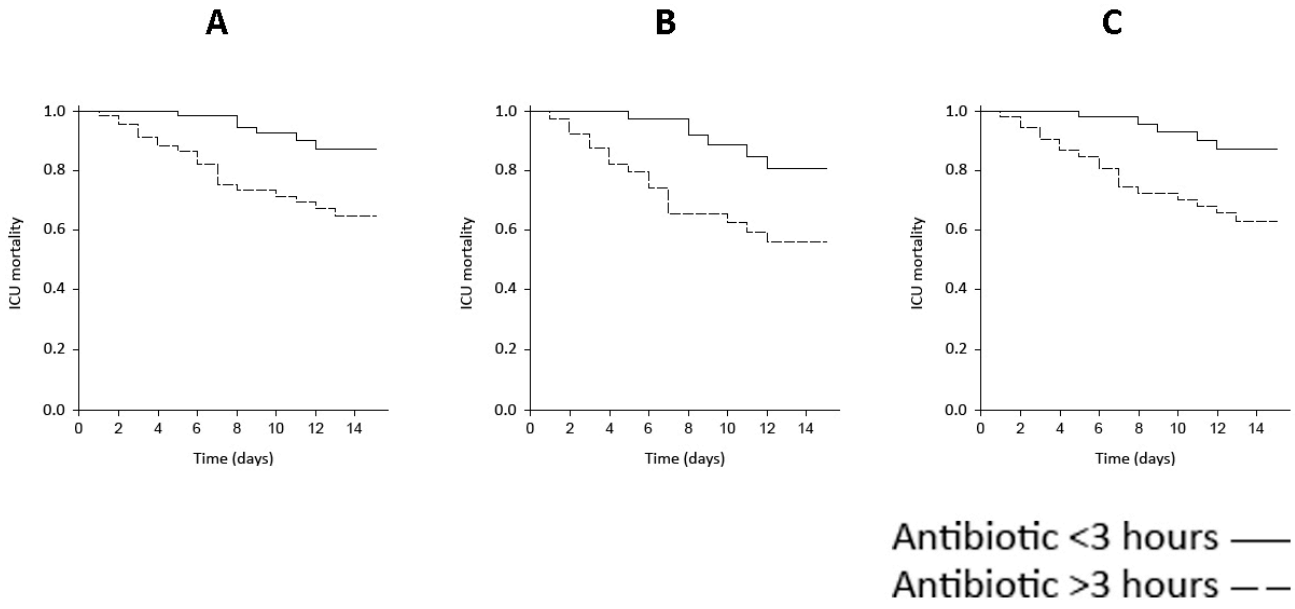
Estudios previos observaron los mismos resultados en pacientes con NAC y shock secundario o bacteriemia (121,123).Nuestros resultados confirman estos hallazgos y, además, sugieren que todos los pacientes con NACG, con o sin shock o necesidad de ventilación mecánica se beneficiarían de tratamiento antibiótico combinado. Aunque pueda parecer una conclusión esperable, una proporción considerable de nuestra muestra recibió monoterapia; de la misma forma, en otros estudios se realizó la misma observación (93-96).

Hoy en día, todavía no está claro cual es la pauta antibiótica empírica óptima en la NACG; algunos autores recomiendan administración de una pauta con macrólido, debido al efecto antiinflamatorio que poseen estas moléculas (84). Sin embargo, no todos los estudios alcanzaron resultados similares. Aunque en nuestra cohorte el tamaño reducido de la muestra hace difícil explorar este asunto, intentamos explorar si la administración de una específica familia de antibióticos se asociaba a diferente mortalidad, en toda la población, y en los subgrupos de pacientes con shock o conectados a VMI, sin obtener diferencias significativas. Además, varios estudios concluyeron que la administración de un régimen con betalactámico asociado a una quinolona condicionaría una supervivencia parecida a un régimen con macrólidos, pero con una mejor tasa de erradicación, una tasa inferior de fracaso de tratamiento y posiblemente menos costes sanitarios (79). Por otro lado, algunos estudios sugieren que la administración de quinolonas se asocie a una mayor aparición de resistencias bacterianas (67). Finalmente, en caso de un entorno social con alta prevalencia de infección respiratoria por *Mycobacterium tuberculosis*, el uso de quinolonas podría enmascarar una tuberculosis pulmonar en vez que una NAC bacteriana (128).

En nuestra muestra la administración de quinolonas mostró una tendencia de menor mortalidad, sin alcanzar diferencias significativas, en toda la cohorte y en los subgrupos de pacientes con shock o conectados a VMI. De acuerdo a los resultados disponibles en la literatura y de los resultados obtenidos en el estudio presente, no es posible recomendar una pauta antibiótica específica.

En 2006, Kumar et al. observaron que en pacientes con shock de cualquier origen la tasa de mortalidad incrementaba al aumentar el tiempo de la primera dosis de antibiótico (89). Estudios posteriores confirmaron estos hallazgos (117). Como se muestra en el análisis Kaplan-Meier (figura 9), la administración precoz de la primera dosis de antibiótico se asoció a reducción de la mortalidad no solo en los pacientes con shock, sino en los pacientes conectados a VMI y en toda la cohorte.

Figura 9: supervivencia en toda la cohorte y en los pacientes con shock y VMI, tras estratificar por antibioticoterapia precoz versus tardía.



En vista de estos resultados, cada paciente que acude a urgencias por NACG bacteriana no neumocócica, debería de recibir la primera dosis de antibióticos durante las primeras 3 horas de la admisión. De hecho, las recomendaciones IDSA/ATS de 2007 recomiendan iniciar el tratamiento antibiótico antes de que el paciente sea trasladado desde urgencias a la planta o a la UCI (36).

Otro aspecto de interés es la asociación que encontramos en el análisis multivariado entre la adherencia a las recomendaciones IDSA/ATS publicadas en 2007 y la reducción de la mortalidad en UCI. Sin embargo, a la hora práctica, las recomendaciones indican administrar de forma precoz un tratamiento antibiótico combinado con familias antibióticas específicas; por esta razón, para explorar de forma más detallada el efecto de simples acciones médicas con respecto a la mortalidad, decidimos separar la variable: "tratamiento adecuado según las recomendaciones IDSA/ATS de 2007" en dos ulteriores variables: "tratamiento antibiótico combinado" y "administración precoz de la primera dosis de antibiótico". Como consecuencia, cuando al modelo multivariado que incluía la variable "tratamiento adecuado según las recomendaciones IDSA/ATS de 2007" se añadían la variables "tratamiento antibiótico combinado" y "administración precoz de la primera dosis de antibiótico", la asociación entre la adherencia a las recomendaciones ya no era significativa. Esto podría sugerir que la suma de acciones que implican la adherencia a las recomendaciones es más importante que investigar la variable "adherencia a las recomendaciones IDSA/ATS de 2007".

En resumen, mediante el presente estudio hemos observado que la mortalidad por neumonía comunitaria grave bacteriana no neumocócica disminuyó entre los dos grupos a estudio; además, la administración de dos antibióticos de forma precoz se asoció a una reducción de la mortalidad, en toda la cohorte y en los subgrupos de pacientes con shock y conectados a VMI. En vista de los resultados obtenidos, todos los pacientes que acuden a urgencias con NACG bacteriana deberían recibir dos antibióticos de forma precoz.

Perspectivas de futuro

Los resultados presentados en esta tesis, así como los datos discutidos, apoyan la administración de dos antibióticos de forma precoz en todos los pacientes que acuden a urgencias con NACG bacteriana neumocócica y no neumocócica. Sin embargo y a la luz de los resultados actuales y de los datos publicados en la literatura, es imposible no plantearse una serie de interrogantes difíciles de responder en este momento y que quedaran pendientes para los años venideros. En este último apartado de la discusión, he querido al menos deliberar sobre varios de estos interrogantes.

¿Hay margen para una ulterior disminución de la mortalidad en los próximos años en la neumonía comunitaria grave bacteriana?

Si bien varios estudios realizados en los años pasados concluyen que la mortalidad por neumonía no ha cambiado significativamente en las últimas décadas (106,107), existen otros artículos que documentan una disminución de la mortalidad en casos de infección grave de forma independiente del foco infeccioso (111-113).

Como ya se ha mencionado, la mayoría de los estudios que investiga la evolución de la mortalidad por neumonía en las últimas décadas se realizaron a partir de análisis retrospectivos de registros demográficos nacionales o internacionales. En este tipo de análisis no se registran datos fundamentales como son la gravedad de la neumonía, la presencia de shock séptico, la necesidad de ventilación mecánica invasiva, la situación clínica global del paciente, la eventual presencia de orden de no realización de RCP. Por estas razones, la interpretación de estos resultados es compleja y debería de realizarse con cautela.

Por otro lado, aunque actualmente se desconocen varios de los mecanismos fisiológicos que se activan en caso de sepsis grave y shock séptico, cada día aumenta el número de artículos que intenta explorar este tema. Estudios sobre la activación e inhibición del sistema inmune (129), los cambios bioquímicos y hormonales (130), y el aumento o disminución de específicos mediadores de la inflamación (131,132), se han publicado. Un estudio reciente identificó variantes genéticas que se asocian a una mayor supervivencia en pacientes con sepsis o shock séptico (133). Además, varios estudios confirmaron disminución de mortalidad en caso de sepsis grave y shock séptico de cualquier foco en consecuencia a una mayor adherencia a las recomendaciones internacionales (114,115), un mejor empleo de los recursos farmacológicos (89,116,117), un mejor manejo de la resucitación del shock séptico (88), un uso más generalizado de ventilación mecánica protectora (118,119) y finalmente una mayor tasa de pacientes no ingresados en UCI por orden de no RCP por presencia de comorbilidades o por presentar un pronóstico muy desfavorable (113).

Debido a la continua evolución de los conocimientos fisiopatológicos de

los pacientes críticos, y gracias a la cada vez mayor disponibilidad de nuevas moléculas farmacológicas, nuevos medicamentos vasopresores e inotropos, nuevas modalidades de ventilación mecánica menos invasivas y con menos efectos adversos, disponibilidad de formulas nutricionales más completas y adaptadas a pacientes críticos, es razonable pensar que sea posible mejorar el cuidado de los pacientes críticos con neumonía comunitaria grave bacteriana, y en consecuencia disminuir su mortalidad.

¿Hay margen para una ulterior disminución de la mortalidad en los próximos años en la neumonía comunitaria grave bacteriana dependiendo del tratamiento antibiótico empírico?

La administración del tratamiento antibiótico empírico en la neumonía comunitaria grave es un momento fundamental en el manejo de la enfermedad. Como previamente observado, varios estudios se publicaron investigando la adherencia a las recomendaciones internacionales, reportando tasas de adherencia de entre un 20 y 100% (93-96). Las causas propuestas para justificar la falta de adherencia fue la diferencia entre el paciente a tratar y el la patología descrita en la recomendación, presencia de insuficiencia renal o hepática, los costes excesivos de algunos antibióticos y la diferencia entre la flora local y las recomendaciones internacionales (97).

Para profundizar conocimientos sobre las causas de falta de adherencia a las guías con respecto al tratamiento antibiótico empírico decidimos realizar un estudio observacional en forma de encuesta clínica dirigida a médicos de UCI y sometiéndole un caso clínico de neumonía comunitaria grave (134). En la encuesta, realizada a 36 médicos empleados en UCI y

con experiencia en enfermedades infecciosas, se pedía indicar el tratamiento empírico en un caso clínico ficticio de NAC. Se registró el número y la familia de antibióticos administrados, y se comparó el resultado con las indicaciones proporcionadas por las recomendaciones IDSA/ATS.

Las pautas de antibióticos más frecuentemente indicadas fueron una asociación entre ceftriaxona/cefotaxima y un macrólido y ceftriaxona/ cefotaxima asociado a una quinolona respiratoria. En la tabla 1 se indican los antibióticos pautados.

Tabla 1: indicación antibiótica en la encuesta clínica.

Antibiotic prescription, dose and duration in the case of community-acquired pneumonia

Antibiotic	N indications	Dose*	Indicated dose ≥ recommendation	Duration < 7 days	Duration 7 - 10 days	Duration > 10 days
Beta-lactams	29/68 (42.7)					
Ceftriaxone	20/68 (29.4)	2.0 (2.0 - 3.5)	19/20 (95.0)	0/20 (0)	17/20 (85.0)	3/20 (15.0)
Cefepime	5/68 (7.4)	6.0 (5.0 - 6.0)	4/5 (80.0)	0/5 (0)	3/5 (60.0)	2/5 (40.0)
Meropenem	4/68 (5.9)	3.0 (1.9 - 3.0)	3/4 (75.0)	0/4 (0)	3/4 (75.0)	1/4 (25.0)
Macrolides	19/68 (27.9)					
Clarithromycin	10/68 (14.7)	1.0 (0.9 - 1.0)	8/10 (80.0)	0/10 (0)	8/10 (80.0)	2/10 (20.0)
Azithromycin	9/68 (13.2)	0.5 (0.5 - 1.0)	9/9 (100)	0/9 (0)	7/9 (77.8)	2/9 (22.2)
Quinolones	8/68 (11.8)					
Levofloxacin	4/68 (5.9)	0.8 (0.6 - 0.8)	3/4 (75.0)	0/4 (0)	4/4 (100)	0/4 (0)
Moxifloxacin	4/68 (5.9)	0.4 (0.4 - 1.3)	4/4 (100)	0/4 (0)	4/4 (100)	0/4 (0)
Glycopeptides	4/68 (5.9)					
Vancomycin	4/68 (5.9)	2.0 (2.0 - 2.0)	4/4 (100)	0/4 (0)	3/4 (75.0)	1/4 (25.0)
Others	8/68 (11.8)					

Results are expressed as the absolute values and percentages: n (%); * result is expressed as the median and interquartile range.

A destacar, en 11 casos sobre 36 (31%) la prescripción fue adecuada con respeto a las indicaciones internacionales. De los 25 episodios de tratamiento no adecuado en 4 se indicó monoterapia, en 10 la pauta antibiótica tenía actividad frente a *Pseudomonas aeruginosa* o *Staphylococcus aureus* meticilina-resistente, mientras que en 11 se indicó la administración combinada de antibióticos no indicados en las recomendaciones (tabla 2).

Tabla 2: adherencia a las recomendaciones internacionales.

Infectious Disease Society of America/American Thoracic Society recommendations and reasons for non-adherence

Clinical case	Adherence to recommendations		Case 1 - Reasons for non-adherence		
	Complied	Not complied	Monotherapy	multiR coverage	Non-indicated AB
Community-acquired pneumonia Case 1	11/36 (30.6)	25/36 (69.4)	4/25 (16.0)	10/25 (40.0)	11/25 (44.0)

Results are expressed as the absolute values and percentages: n (%). multiR - multi-resistant; AB - antibiotic;

Estas conclusiones, en línea con los resultados obtenidos en otros estudios (93-96), tiene implicaciones muy importantes ya que, como se ha mencionado previamente, una baja adherencia a las recomendaciones terapéuticas se asocia a mayor morbilidad y mortalidad, así como a un aumento en los costes sanitarios (88,92).

¿Cual es el mecanismo que justifica una reducción de la mortalidad tras administración de tratamiento antibiótico combinado en la neumonía comunitaria grave bacteriana, y cuál es la asociación óptima para asegurar una disminución de la mortalidad en la NACG bacteriana?

El argumento más importante para justificar la administración de antibioticoterapia combinada en pacientes con neumonía es cubrir de forma empírica microorganismos típicos y atípicos. Sin embargo, varios estudios obtuvieron resultados contrastantes y en formas leves y moderadas de neumonía la administración de monoterapia ha demostrado asociarse a la misma mortalidad cuando comparado con antibioticoterapia combinada.

Pacientes con neumonía leve a moderada que presentan factores de riesgo de mala evolución clínica, pacientes con neumonía y bacteriemia son los que más se benefician de tratamiento antibiótico combinado, en este caso la cobertura de microorganismos atípicos con tratamiento

combinado se asoció a menos costes de tratamiento, mayor tasa de erradicación microbiológica y resolución clínica, y disminución de la mortalidad (135). Un ensayo clínico recién publicado no encontró diferencias en mortalidad tras comparar pacientes con neumonía comunitaria con PSI score de IV o V que recibían moxifloxacino comparado con una pauta de tratamiento antibiótico combinado; sin embargo, el porcentaje de pacientes con shock o conectados a VMI era escasa, y no todos los pacientes eran ingresados en UCI (79). Por otro lado, en el caso de pacientes con neumonía ingresados en UCI, y especialmente en los subgrupos de pacientes con shock secundario, el uso de tratamiento combinado en general se asociaba a una mortalidad inferior; se demostró que la falta de cobertura para microorganismos atípicos en caso de neumonía comunitaria que requiere ingreso en UCI se asocia a mayor mortalidad (136).

Además de la cobertura de agentes atípicos, otras hipótesis fueron propuestas para justificar la disminución de la mortalidad, cuales la cobertura de microorganismos no identificados en los cultivos, el efecto sinérgico de algunas pautas antibióticas, una más rápida disminución de la carga bacteriana, el efecto antiinflamatorio que poseen algunos antimicrobianos (137).

En vista de los resultados obtenidos en nuestro análisis, parece poco probable que la cobertura de agentes no identificados en los cultivos sea la causa de la disminución de la mortalidad. Los estudios CAPUCI I y II se realizaron con la finalidad de profundizar los conocimientos en la neumonía comunitaria grave, y estudiar las características del tratamiento antibiótico para intentar mejorar el cuidado de nuestros pacientes. Aunque el manejo del paciente no estaba estandarizado ni

protocolizado, el esfuerzo diagnóstico para identificar el microorganismo era considerable, con un promedio de 2 a 3 muestras recogida por cada pacientes (datos no presentes en las tablas). En consecuencia, es poco probable que muchos pacientes tuvieran co-infecciones por microorganismos no identificados.

Tras realizar una revisión de la literatura, no se encontraron estudios que valoraban in vivo posibles sinergias antibióticas en individuos con neumonía comunitaria; por otro lado, escasos estudios valoran la sinergia antibiótica, y en general no se encontraron pautas antibióticas útiles para el tratamiento de la neumonía que presenten un efecto sinérgico. De la misma forma, no identificamos en la literatura estudios finalizados a estudiar el cambio de la carga bacteriana tras la administración de regímenes de antibióticos en monoterapia o de tratamiento combinado.

Finalmente, varios estudios realizados in vitro e in vivo (84,85) concluyeron que la administración de una asociación con macrólido se asocia a una reducción de la mortalidad, y que esta asociación podría ser condicionada al efecto antiinflamatorio que se demostró poseer la familia de los macrólidos (138). Si bien no todos los estudios realizados en pacientes críticos confirmen esta asociación, se podría postular que los casos que más se benefician del efecto antiinflamatorio de los macrólido sean aquello pacientes con un elevado estado proinflamatorio, que podrían representar un subgrupo de los pacientes con shock. Desafortunadamente, no existen en la actualidad ensayos clínicos aleatorizados finalizados al estudio de este aspecto. Aunque de momento no hay evidencia suficiente para recomendar una pauta antibiótica específica, un metaanálisis publicado en 2014 por Sligl et al.

(84) que incluye 28 estudios observacionales realizados en pacientes ingresados en UCI concluye que la asociación de un betalactámico y un macrólido es la pauta que se asocia a menos mortalidad.

¿Cual es el mecanismo que justifica una reducción de la mortalidad tras la administración de tratamiento antibiótico precoz?

En 2006, Kumar et al. publicaron un estudio realizado en pacientes con shock séptico de cualquier foco, concluyendo que al aumentar el tiempo de retraso de la administración de la primera dosis de antibiótico se asociaba con un aumento linear de la mortalidad (89). Previamente varios estudios realizados en modelos animales obtuvieron las mismas conclusiones. Además, varios estudios sugirieron una ventana de tiempo limitada para el tratamiento eficaz del shock, de cualquier tipo. El estudio de Wiggers (139), publicado hace años, demostró que en animales con shock hemorrágico la posibilidad de recuperación disminuía con el pasar de las horas, siendo imposible alcanzarla tras transcurrir varias horas del inicio del shock. En general, en la práctica clínica diaria, son muchas las situaciones en que el tiempo es fundamental: shock hipovolémico en el paciente traumatológico (140), shock cardiogénico tras el infarto de miocardio (141), y shock obstructivo en caso de trombo-embolismo pulmonar masivo (142).

En el caso de neumonía grave, con shock o sin shock, el mecanismo que justifica la disminución de mortalidad tras administración precoz de la primera dosis de antibiótico podría ser el mismo postulado en los estudios anteriores: intervenir con medidas farmacológicas ante una situación en que los mecanismos de defensa del organismo no podrían

compensar el desajuste fisiológico, a causa de la gravedad de la patología o por la debilidad de las defensas.

¿Cual es el impacto del tratamiento antibiótico combinado sobre la emergencia de nuevas resistencias a antibióticos?

Si bien hay muchos mecanismos que conducen a la aparición de nuevas resistencias bacterianas, una excesiva presión antibiótica y un uso inadecuado de moléculas antibióticos representan los factores de riesgo de mayor peso para la aparición de nuevas resistencias.

Por un lado, aunque las quinolonas en algunos estudios han demostrado un mayor poder de erradicación microbiológica (143), una más efectiva tasa de curación clínica (144) y posiblemente menos costes de tratamiento (145,146), parece que la tasa de nuevas resistencias bacterianas aumente tras empleo de quinolonas comparado con otras familias de antibióticos (67). Además, en caso de contexto social con elevada tasa de tuberculosis pulmonar, la administración de quinolonas como tratamiento empírico de una neumonía, podría enmascarar un tuberculosis pulmonar, con el riesgo de un tratamiento no adecuado y el desarrollo de cepas de *Mycobacterium tuberculosis* multirresistente (128).

Tras revisar en la literatura científica, el único estudio que encontramos que compara desenlaces clínicos en neumonía grave tras administración de monoterapia o terapia combinada, y que explora el desarrollo de resistencias en función de la pauta recibida, no encontró diferencias en cuando a nuevas resistencias después de administrar uno o dos antibióticos (83). Nuevos estudios finalizados a explorar este tema deberían de realizarse para aclarar un tema tan importante.

VII. LIMITACIONES

LIMITACIONES

El trabajo que aquí se ha presentado tiene una serie de limitaciones que deben mencionarse.

La primera de ellas es la naturaleza observacional del estudio. De hecho, la prescripción de los antibióticos y todas las acciones médicas para el manejo clínico de la neumonía no fueron estandarizadas y fueron establecidas por el médico responsable del paciente. Por otro lado, de cara a minimizar este problema se realizó un estudio control con apareamiento exacto, de forma que las características clínicas más relevantes de cara a los desenlaces clínicos eran superponibles (tablas 1 y 2 del estudio 1, tabla 1 y 2 del estudio 2). Además, para evitar un sesgo de selección se comparó la mortalidad entre los pacientes seleccionados para el apareamiento y los restantes pacientes del grupo de pertenencia, sin observarse diferencias significativas (figura 1 de artículo 1 y figura 2 de artículo 2).

Otra limitación significativa es que en los últimos años se han implementado mejoras significativas en cuanto al cuidado de los pacientes críticos. Aspectos como son una mejor resucitación de la sepsis grave y del shock séptico, una VMI menos agresiva y asociada a menos complicaciones, una más rápida y eficaz nutrición, la disponibilidad de nuevos fármacos antimicrobianos y no antimicrobianos ha permitido disminuir la mortalidad global de los pacientes ingresados en UCI. Aunque los mayores determinantes de mortalidad fueron introducidos como co-variadas en el análisis multivariado, no fue posible introducir todas las variables que podrían jugar un papel significativo en la disminución de la mortalidad.

El riesgo estimado de fallecimiento se estimó de forma diferente en las dos cohortes; en el estudio CAPUCI I se usó la escala APACHE II, mientras que en e CAPUCI II se usó la escala SAPS III. Las dos escalas fueron validadas en amplias cohortes procedentes de diferentes regiones de mundo (147,148). Tras estimar el riesgo de fallecimiento mediante las dos escalas creamos una variable llamada "riesgo estimado de fallecimiento", que permitió comparar la mortalidad prevista entre los dos grupos.

A destacar que las UCI que participaron al estudio CAPUCI I no son las mismas del CAPUCI II; en el primer estudio participaron 33 UCIs españolas mientras que el estudio CAPUCI II fue llevado a cabo en 29 UCIs de Europa, 24 desde España y 5 Europeas. Esto podría condicionar un sesgo de selección de pacientes. De todas maneras, después de realizar el apareamiento de pacientes, en ambos artículos publicados, observamos que todos los pacientes procedentes del estudio CAPUCI II procedían de UCIs españolas. De esta forma, el riesgo de sesgo de selección de pacientes es mínimo y no debería de afectar a los resultados.

VIII. CONCLUSIONES

CONCLUSIONES

Como conclusión, el presente trabajo documenta una reducción de la mortalidad por neumonía comunitaria grave bacteriana neumocócica y no neumocócica entre los dos períodos a estudio. Además, la administración precoz de la primera dosis de antibiótico y la administración de antibioticoterapia empírica combinada presentaron una asociación positiva con la disminución de la mortalidad en UCI.

Objetivo principal

Explorar si en las últimas décadas hubo cambios en la tasa de mortalidad por neumonía bacteriana grave adquirida en la comunidad.

La tasa de mortalidad en UCI presentó una significativa reducción entre los dos períodos a estudio. En caso de neumonía neumocócica grave la disminución de mortalidad entre el período 2000-2002 y el período 2008-2014 fue de un 15%; en caso de neumonía bacteriana no neumocócica la disminución fue de un 17%.

Esta tendencia se confirmó en toda la cohorte y en los subgrupos de pacientes con shock séptico secundario y conectados a ventilación mecánica.

Objetivo secundario

Estudiar si la administración de dos antibióticos se asocia a una disminución de la mortalidad en pacientes con neumonía comunitaria bacteriana grave.

En caso de neumonía bacteriana grave neumocócica y no neumocócica se observó disminución de la tasa de mortalidad tras administración de dos antibióticos. Esta tendencia se confirmó en toda la cohorte y en los

subgrupos de pacientes con shock séptico secundario y en pacientes conectados a ventilación mecánica invasiva. A la luz de los resultados obtenidos todo paciente que acude a urgencias con neumonía comunitaria grave bacteriana, neumocócica o no neumocócica, debería de recibir dos antibióticos de forma empírica. Dependiendo de la evidencia actualmente disponible en la literatura, no existe una pauta superior a otra, aunque parece que la administración de una asociación de un betalactámico y un macrólido podría ser la más adecuada.

Objetivo terciario

Estudiar si la administración precoz de la antibioticoterapia empírica se asocia a una disminución de la mortalidad en pacientes con neumonía comunitaria bacteriana grave.

En caso de neumonía bacteriana grave neumocócica y no neumocócica la administración de la primera dosis de antibiótico durante las primeras tres horas tras la llegada a urgencias se asoció a disminución de la mortalidad. Esta tendencia se confirmó en toda la cohorte y en los subgrupos de pacientes con shock y conectados a ventilación mecánica invasiva. Frente a los resultados obtenidos, cualquier paciente que acude a urgencias con neumonía comunitaria grave bacteriana, neumocócica y no neumocócica, debería de recibir la primera dosis de antibiótico durante las primeras tres horas de la admisión. La recogida de muestras microbiológicas no debería de retrasar el comienzo de la antibioticoterapia.

XI. BIBLIOGRAFÍA

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X. ANEXOS

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ORIGINAL

Community-acquired Legionella Pneumonia in the intensive care unit: Impact on survival of combined antibiotic therapy

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KEYWORDS
Severe community-acquired pneumonia;
Legionella pneumophila;
Legionnaires' disease;
Combined antibiotic therapy

Abstract
Objectives: To compare intensive care unit (ICU) mortality in patients with severe community-acquired pneumonia (SCAP) caused by *Legionella pneumophila* receiving combined therapy or monotherapy.
Methods: A prospective multicenter study was made, including all patients with sporadic, community-acquired Legionnaires' disease (LD) admitted to the ICU. Admission data and information on the course of the disease were recorded. Antibiotic prescriptions were left to the discretion of the attending physician and were not standardized.
Results: Twenty-five cases of SCAP due to *L. pneumophila* were included, and 7 patients (28%) out of 25 died after a median of 7 days of mechanical ventilation. Fifteen patients (60%) presented shock. Levofloxacin and clarithromycin were the antibiotics most commonly used in monotherapy, while the most frequent combination was rifampicin plus clarithromycin. Patients subjected to combination therapy presented a lower mortality rate versus patients subjected to monotherapy (odds ratio for death [OR] 0.15; 95%CI 0.02–1.04; $p = 0.08$). In patients with shock, this association was stronger and proved statistically significant (OR for death 0.06; 95%CI 0.004–0.86; $p = 0.04$).

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Conclusions: Combined antibiotic therapy decreases mortality in patients with SCAP and shock caused by *L. pneumophila*.

PALABRAS CLAVE
Neumonia comunitaria grave;
Legionella pneumophila;
Enfermedad del Legionario;
Tratamiento antibiotico combinado

Neumonía por legionella intrahospitalaria en la unidad de cuidados intensivos: impacto sobre la supervivencia de la terapia antibiótica combinada

Resumen
Objetivos: comparar la mortalidad de los pacientes ingresados en unidad de cuidados intensivos (UCI) por neumonía comunitaria severa (NCS) causada por *Legionella pneumophila* que recibieron tratamiento combinado o monoterapia.
Metodos: estudio prospectivo multicentrico que incluye los pacientes con Enfermedad del Legionario comunitaria, esporádica, que requiere ingreso en UCI. Se recogieron datos en el momento del ingreso y durante la evolución en la UCI. El tipo y el numero de antibióticos a administrar no fue estandardizado y fue decidido por el medico responsable del paciente.
Resultados: se incluyeron veinticinco casos de NCS causada por *Legionella pneumophila*, 7 pacientes (28%) de los 25 falleció tras una mediana de 7 días de ventilación mecánica. Quince pacientes (60%) presentaron shock. Los antibióticos mas prescritos en monoterapia fueron levofloxacino y claritromicina, mientras que la asociación mas frecuente fue rifampicina mas claritromicina. Los pacientes que recibieron tratamiento combinado presentaron una mortalidad inferior con respecto a los tratados con monoterapia (odds ratio para fallecimiento [OR] 0.15; IC95% 0.02 hasta 1.04; p = 0.08). En el subgrupo de pacientes con shock la asociación fue mas fuerte y estadísticamente significativa (OR para fallecimiento 0.06; IC95% 0.004 hasta 0.86; p = 0.04).
Conclusiones: el tratamiento antibiótico combinado disminuye la mortalidad de los pacientes con NCS y shock causados por *Legionella pneumophila*.

Introduction

In patients with SCAP admitted to the ICU, mortality ranges from 25% to 40%.[1–4] In many series, *Legionella* spp. ranks second after *Streptococcus pneumoniae* in the list of causative agents of SCAP.[5–9] The incidence of legionellosis has increased in the United States for the last decades.[10] Although it has been suggested that a presumptive diagnosis of LD may be done even in cases of SCAP, most authors believe that clinical and laboratory features of LD are not distinctive[5–9,11–13]; that is why empiric coverage of *Legionella* spp. is strongly recommended in most international guidelines for management of SCAP.[1–4,13] Once *Legionella pneumophila* has been confirmed as the etiologic agent of severe pneumonia some experts suggest that combined therapy would be preferable to monotherapy, although there is no solid evidence to confirm it.[1–9,11–15] In case of combined therapy, macrolide or fluoroquinolone in addition with rifampicin is the approach that is usually suggested; again, scientific evidence supporting this assertion is scarce.[14,16] To the best of our knowledge, only a few monocentric and retrospective studies have focused on ICU patients with SCAP due to *L. pneumophila*.[17–21] Our hypothesis was that combination antibiotic therapy improves outcome in critically ill patients with SCAP caused by *L. pneumophila*; the primary outcome of the present study was to compare ICU mortality; the analysis was done in all patients admitted to the ICU and subsequently only in patients with shock. Secondary objectives were to document the epidemiology and therapeutic options.

Patients and methods

CAPUCI study collected all patients admitted for SCAP to thirty-three hospitals in Spain, from December 1st 2000 to February 28th 2002.[22] In CAPUCI2 study, an ECCRN endorsed project, data were recorded from patients admitted to ICU for SCAP, from 2008 to 2011. We analyzed patients enrolled in these large series to gain insight into the current therapy and outcomes for severe CAP admitted in the ICU caused by *L. pneumophila*. Informed consent was waived by the ethics committee due to the observational nature of the study. Patients were admitted to the ICU either to undergo mechanical ventilation or because they were in an unstable condition requiring intensive medical care.[23] Patients with severe chronic illness in whom pneumonia was an expected terminal event were not included. At least one of the following tests was required to establish a diagnosis of LD: isolation of *L. pneumophila* from any respiratory sample culture on buffered charcoal yeast extract selective medium; a positive detection of urinary antigen test by enzyme immunoassay; an indirect immunofluorescent antibody test showing a fourfold increase in IgG antibodies, using a commercial ELISA kit against *L. pneumophila*. The antibiotic prescriptions and the decision to initiate monotherapy or combination therapy were left to the discretion of the attending physician and were not protocolized. Patients were observed until death or ICU discharge. Data of antibiotic doses were not registered.

Definitions

CAP was defined as an acute lower respiratory tract infection characterized by: (1) an acute pulmonary infiltrate on chest X-ray, (2) confirmatory findings of a clinical examination, and (3) acquisition of the infection outside of a hospital, long-term care facility, or nursing home. Diagnosis of active smoker, alcoholism and chronic obstructive pulmonary disease (COPD) was done with criteria reported elsewhere.[24,25] Immunocompromise was defined as primary immunodeficiency or immunodeficiency secondary to radiation treatment, use of cytotoxic drugs or steroids (daily doses of >20 mg of prednisolone or equivalent for >2 weeks),[26] or AIDS. Shock was defined as the need for vasopressor during >4 h after fluid replacement; rapid radiographic spread was defined as an increase in the size of opacities on chest radiograph by >50% at 48 h. Monotherapy was defined as administration of the same single antibiotic during the first 2 days of ICU admission. Combination therapy was defined as administration of the same two antibiotics within the first 2 days of ICU admission.

Statistical analysis

ICU mortality was chosen as primary endpoint. All data spreadsheets, analysis codes and outputs, were electronically stored and archived. Data validation consisted of searching out-of-range and missing values, and lack of consistency between related variables detection. General characteristics obtained at baseline, risk factors and other variables were compared and summarized. Qualitative variables were summarized using absolute and relative frequencies for each group. Differences between groups were tested using Fisher's exact test. Quantitative variables were summarized using mean, standard deviation and valid cases for each group. Differences between groups were tested using Mann–Whitney–Wilcoxon test. The Kaplan–Meier product limit method was used to construct survival curves for patients receiving combination and monotherapy regimens. All statistical decisions were based on a significance level of 5%. All data management and statistical analysis were performed using SPSS 15.0 (SPSS Inc., Chicago, IL, USA).

Results

Data from 779 ICU patients with SCAP were extracted. A total of 25 patients with diagnosis of *L. pneumophila* pneumonia were recruited, of whom 15 (60%) presented with shock on admission. All patients presented sporadic forms of Legionnaires' disease. Seven patients (28%) out of 25 died after a median of 7 days of mechanical ventilation; all deceases were secondary to multi-organ failure and were pneumonia-related. Median age of the patients was 55 years and median APACHE II score was 19. Thirteen patients (52%) were smokers. The commonest comorbitiy conditions were: cardiomyopathy (32%) and diabetes mellitus (20%). Nineteen patients (76%) required MV. Age was significantly similar in patients with shock and without shock. Mean APACHE II score and length of stay had a trend to be higher in group of patients with shock, but without achieving significant statistic differences. Need for mechanical ventilation, rapid radiographic spread and ICU mortality was significantly higher in the shock subset. Acute kidney injury was documented in 2 patients (8%). Other baseline characteristics of the study population are described in Table 1. Table 2 shows the diagnostic methods used for detecting infection by *Legionella* spp.; 87.5% of patients were positive for antigen urinary detection.

Ten patients were treated with monotherapy and 50% of this group died: levofloxacin and clarithromycin were the most administered antibiotics; each medication was

Table 1 Demographic characteristics of the study population.

Variable	Shock ($n=15$)	No shock ($n=10$)	Total ($n=25$)	p-Value
Age mean years, (SD)	54.7 (15.3)	53.7 (14.5)	54.3 (14.7)	0.91
Age >55 years, (n) %	7 (46.7)	6 (60.0)	13 (52.0)	0.69
Male gender, (n) %	11 (73.3)	7 (70.0)	18 (72.0)	1.00
Mean APACHE II score, (SD)	20.1 (6.3)	16.4 (4.1)	18.6 (5.8)	0.11
APACHE II score >15, (n) %	12 (80.0)	7 (70.0)	19 (76.0)	0.65
Length of stay, (SD)[a]	27.2 (22.6)	17.6 (17.5)	23.4 (20.9)	0.43
Comorbidity/risk factors, (n) %				
Smoking	7 (46.7)	6 (60.0)	13 (52.0)	0.69
Alcohol use	4 (26.7)	3 (30.0)	7 (28.0)	1.00
Immunocompromise	3(20.0)	0(0)	3 (12.0)	0.25
COPD	1 (6.7)	3 (30.0)	4 (16.0)	0.27
Cardiomyopathy	6 (40.0)	2 (20.0)	8 (32.0)	0.40
Diabetes mellitus	4 (26.7)	1 (10.0)	5 (20.0)	0.62
Mechanical ventilation, *n* (%)	14 (93.3)	5 (50.0)	19 (76.0)	0.02
Rapid radiographic spread, *n* (%)	14 (93.3)	5 (50.0)	19 (76.0)	0.02
Combined therapy, *n* (%)	9 (60.0)	6 (60.0)	15 (60.0)	1.00
ICU mortality rate, *n* (%)	7 (46.7)	0(0)	7 (28.0)	0.02

APACHE, acute physiology and chronic health evaluation; ICU, intensive care unit; COPD, chronic obstructive pulmonary disease.
[a] Only for survivors.

Table 2 Yield of diagnostic tests for 25 patients with severe Legionnaires' disease admitted to the ICU.

Test	No. of performed test	No. of positive results, *n* (%)
Urine antigen detection	24	21 (87.5)
Sputum culture	16	4 (25.0)
Bronchoscopic samples culture	15	5 (33.3)
Pleural fluid culture	3	1 (33.3)
Serology	13	8 (53.3)

ICU, intensive care unit.

prescribed in 4 patients. All patients treated with levofloxacin died while only 1 patient of 4 who received clarithromycin did not survive. Fifteen patients received combined therapy; 2 patients out of 15 expired. The most used combination therapy was rifampicin and clarithromycin, this combination was given in 3 patients: 1 person out of 3 who received this combination died. The second most used combined therapy were: clarithromycin, ciprofloxacin plus rifampicin, and clarithromycin, levofloxacin plus rifampicin. Each one the previous combinations was administered in 2 patients. One patient expired after being treated with clarithromycin, ciprofloxacin and rifampicin.

The characteristics of patients who received monotherapy or combination therapy are shown in Table 3. Patients who received combination therapy presented a lower ICU mortality rate versus patients treated with monotherapy (OR of death 0.15; 95%CI 0.02–1.04; $p = 0.08$). When the analysis was done in patients with shock, the association between combination therapy and decrease of mortality was stronger with statistical significance (OR of death 0.06; 95% CI 0.004–0.86; $p = 0.04$). The demographics for the patients with shock who received combination therapy versus monotherapy were comparable, as shown in Table 4. Survival time for patients receiving combination therapy versus monotherapy is represented ($p = 0.04$) using a Kaplan–Meier survival curve (Fig. 1).

Discussion

This is the first study reporting that patients with legionellosis and shock can benefit from two agents instead of one. Moreover, to our knowledge, this is the largest series of SCAP by *L. pneumophila* in ICU patients that was analyzed in a prospective, multicentric study: previous studies were usually monocentric and retrospective.[14,17–21] Furthermore, our population was homogeneous since all patients fulfilled inclusion criteria of sporadic, community-acquired LD.[27] A generalized pitfall of previous series on severe LD is that *Legionella* antigen detection was not used as part of diagnostic methods. This drawback should be taken into account since it has been suggested that positive urine antigen detection could be associated with a more severe form of the disease.[28]

Results from at least two studies demonstrated that combined antibiotic therapy improve survival in

Table 3 Characteristics of 25 patients with SCAP caused by *Legionella pneumophila* receiving combination therapy or monotherapy.

Variable	Combined therapy ($n = 15$)	Monotherapy ($n = 10$)	*p*-Value
Age, mean years, (SD)	51.2 (14.9)	59.0 (13.7)	0.18
Age >55 years, (n) %	6 (40.0)	7 (70.0)	0.23
Male sex, (n) %	11 (73.3)	7 (70.0)	1.00
Mean APACHE II score, (SD)	17.9 (5.6)	19.7 (6.1)	0.31
APACHE II score >15, (n) %	11 (73.3)	8 (80.0)	1.00
Length of stay, (SD)[a]	27.4 (23.4)	16.5 (15.1)	0.18
Comorbidity/risk factor, n (%)			
Smoking	9 (60.0)	4 (40.0)	0.43
Alcohol use	4 (26.7)	3 (30.0)	1.00
Immunocompromise	1 (6.7)	2 (20.0)	0.54
COPD	2 (13.3)	2 (20.0)	1.00
Cardiomyopathy	3 (20.0)	5 (50.0)	0.19
Diabetes mellitus	2 (13.3)	3 (30.0)	0.36
Mechanical ventilation, (*n*) %	11 (73.3)	7 (70.0)	1.00
Rapid radiographic spread, *n* (%)	13 (92.9)	6 (60.0)	0.12
Shock, *n* (%)	9 (60.0)	6 (60.0)	1.00
ICU mortality rate, *n* (%)	2 (13.3)	5 (50.0)	0.08

SCAP, severe community-acquired pneumonia; APACHE, acute physiology and chronic health evaluation; ICU, intensive care unit; COPD, chronic obstructive pulmonary disease.

[a] Only for survivors.

Table 4 Characteristics of 15 patients with SCAP caused by *Legionella pneumophila* and shock receiving combination therapy or monotherapy.

Variable	Combined therapy ($n=9$)	Monotherapy ($n=6$)	p-Value
Age, mean years, (SD)	50.2 (13.4)	61.5 (16.6)	0.22
Age >55 years, (n) %	3 (33.3)	4 (66.7)	0.32
Male sex, (n) %	7 (77.8)	4 (66.7)	1.00
Mean APACHE II score, (SD)	18.3 (7.1)	22.7 (4.2)	0.18
APACHE score >15, (n) %	6 (66.7)	6 (100)	0.23
Length of stay, (SD)[a]	31.4 (25.3)	20.8 (18.1)	0.53
Comorbidity/risk factor, n (%)			
Smoking	6 (66.7)	1 (16.7)	0.12
Alcohol use	3 (33.3)	1 (16.7)	0.60
Immunocompromise	1 (11.1)	2 (33.3)	0.53
COPD	1 (11.1)	0 (0)	1.00
Cardiomyopathy	3 (33.3)	3 (50.0)	0.62
Diabetes mellitus	2 (22.2)	2 (33.3)	1.00
Mechanical ventilation, (*n*) %	8 (88.9)	6 (100)	1.00
Rapid radiographic spread, *n* (%)	9 (100)	5 (83.3)	0.40
ICU mortality rate, *n* (%)	2 (22.2)	5 (83.3)	0.04

SCAP, severe community-acquired pneumonia; APACHE, acute physiology and chronic health evaluation; ICU, intensive care unit; COPD, chronic obstructive pulmonary disease.
[a] Only for survivors.

critically ill patients with severe infection and shock.[29,30] A recent study including mild-to-moderate LD in 49 cancer patients confirms that combination therapy is correlated with better outcome, especially in patients with severe pneumonia.[31] Gacouin et al. reported in 2002 a retrospective series of 43 cases of severe *Legionella* spp. pneumonia admitted to the ICU: authors concluded that combined treatment with quinolones was the best therapeutic option for severe LD.[21] Data from our study suggest that combination therapy is better than monotherapy in the setting of SCAP by *L. pneumophila* in patients with shock.

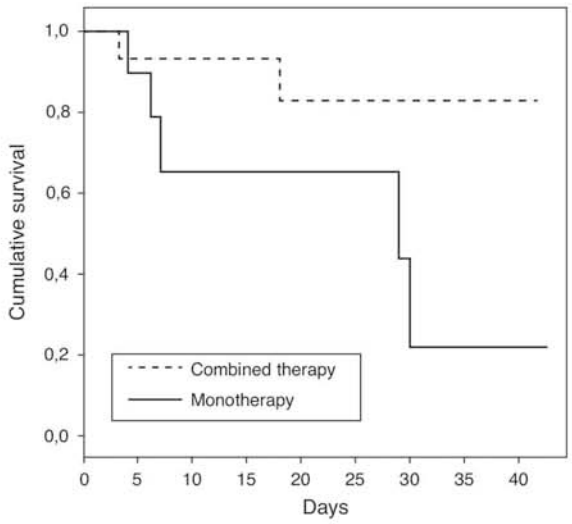

Figure 1 Kaplan–Meier survival curve for patients with shock receiving combination therapy versus monotherapy censored at 40 days (log rank test: p value = 0.04).

Laboratory and experimental data support the concept that both fluoroquinolones and newer macrolide/azalides agents against *L. pneumophila* are superior to erythromycin.[5–7,14,32] Azithromycin, an excellent therapeutic option in severe LD,[5–7,14,32–34] was administered in only one patient. The reason is because azithromycin was not available in Spain when the CAPUCI study was realized. The patient who received azithromycin was enrolled in CAPUCI II study.

In our series, differently to prior similar studies, new fluoroquinolones or macrolides were administered in all cases. Clarithromycin has been found to be an effective anti-*Legionella* agent in non-severe LD, but clinical efficacy in the setting of the ICU has not been established until now.[14,35,36] Three patients out of four who received clarithromycin survived. Although the small number of patients in our series is clearly a major drawback, our results suggest that clarithromycin could be a good therapeutic agent in severe LD.

Recent studies suggest that levofloxacin should be the drug of choice for the treatment of mild-to-moderate LD[35,37,38]; on the other hand, there is certain lack of consistency about its use in monotherapy in severe cases of LD, especially when mechanical ventilation is needed.[14,35–37] The finding of death in our four patients exclusively treated with levofloxacin raises some concerns on its use in monotherapy in this subset of severely ill patients, although the small number of patients does not allow definitive conclusions. Controversy between new macrolides versus fluoroquinolones as treatment of choice of severe LD is beyond the scope of this discussion since this study was not designed to focus on this issue.

Rifampicin is very active against *L. pneumophila* both in vitro and in animal model[5,14]; however, its clinical use in monotherapy has been precluded because of concerns of increased resistance to the drug. Nevertheless, at least

one study in an animal model denied an increase in antibiotic resistance.[39] Experimental data in animal models show that the bacterial killing rate is dramatically higher when rifampicin is added to other antibiotic.[40] The association of macrolides and rifampicin has been the recommended combined therapy for treating severe LD.[5,14] On the contrary, in cases of non-severe LD, this association was not superior versus monotherapy.[36]

There are some limitations to our study. First, as with other publications exploring this issue, results are not from a randomized controlled study. Second is the small sample size; however, it is unlikely that an adequate comparative clinical trial could be completed. Data for our study were collected from two different chronological periods so there may be confounding factors that cannot be corrected nor adjusted. Another relevant limitation is that azithromycin, an excellent therapeutic option for treating severe LD, was only administered in one patient because it was not available in Spain in intravenous formulation until recently. Finally, delay of antibiotic therapy from pneumonia onset was not recorded. Newer studies should be performed comparing recent antibiotics, but this is not feasible due to the small number of patients currently complicated with MV.

Conclusions

In summary, our findings show a reduction of ICU mortality in patients with SCAP caused by *L. pneumophila* and shock, when combined therapy is administered instead of monotherapy. Our results are consistent with other observational studies suggesting that combination therapy improves survival in the subset of the most severe critically ill patients with SCAP.

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Conflicts of interest

Dr Rello serves in the speaker's bureau and advisory boards for Pfizer. The remaining authors declared no conflicts of interest.

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Annex 1.

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Causes of non-adherence to therapeutic guidelines in severe community-acquired pneumonia

Causas de la falta de adherencia a las guías terapéuticas para la neumonía grave

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ABSTRACT

Objective: To assess the adherence to Infectious Disease Society of America/American Thoracic Society guidelines and the causes of lack of adherence during empirical antibiotic prescription in severe pneumonia in Latin America.

Methods: A clinical questionnaire was submitted to 36 physicians from Latin America; they were asked to indicate the empirical treatment in two fictitious cases of severe respiratory infection: community-acquired pneumonia and nosocomial pneumonia.

Results: In the case of community-acquired pneumonia, 11 prescriptions of 36 (30.6%) were compliant with international guidelines. The causes for non-compliant treatment were monotherapy (16.0%), the unnecessary prescription of broad-spectrum antibiotics (40.0%) and the use of non-recommended antibiotics (44.0%).

In the case of nosocomial pneumonia, the rate of adherence to the Infectious Disease Society of America/American Thoracic Society guidelines was 2.8% (1 patient of 36). The reasons for lack of compliance were monotherapy (14.3%) and a lack of dual antibiotic coverage against *Pseudomonas aeruginosa* (85.7%). If monotherapy with an antipseudomonal antibiotic was considered adequate, the antibiotic treatment would be adequate in 100% of the total prescriptions.

Conclusion: The compliance rate with the Infectious Disease Society of America/American Thoracic Society guidelines in the community-acquired pneumonia scenario was 30.6%; the most frequent cause of lack of compliance was the indication of monotherapy. In the case of nosocomial pneumonia, the compliance rate with the guidelines was 2.8%, and the most important cause of non-adherence was lack of combined antipseudomonal therapy. If the use of monotherapy with an antipseudomonal antibiotic was considered the correct option, the treatment would be adequate in 100% of the prescriptions.

Keywords: Community-acquired pneumonia/drug therapy; Pneumonia ventilator-associated/drug therapy; Anti-bacterial agents/therapeutic use; Advance directive adherence

INTRODUCTION

Acute respiratory infection is associated with high morbidity and social costs,[1,2] which significantly increase in complicated cases with septic shock.[3,4] Antibiotic therapy is one of the most effective tools for reducing mortality.[4] The association between the administration of inadequate antibiotics in the case of respiratory septic shock and a significant increase in both morbimortality[5-7] and multi-drug resistance has been extensively described.[8]

Several scientific societies have published therapeutic and clinical management recommendations, with the guidelines published by the Infectious Disease Society of America/American Thoracic Society (IDSA/ATS) serving as a reference in Latin America.[9,10]

Various studies conducted in Europe,[11,12] the United States[13] and Australia[14] have analyzed adherence to therapeutic guidelines in empirical antibiotic prescription. However, no similar studies have been performed in Latin America.

In the present study, adherence to IDSA/ATS indications for the treatment of severe pneumonia and the causes of non-compliance with the recommendations were analyzed.

METHODS

A survey was administered to 36 Latin American physicians with extensive experience in the intensive care unit (ICU). The survey was administered during a course on antibiotic politics for critical care patients, which took place in the Hospital Vall d' Hebron, Barcelona, Spain, in May and July of 2013. The same questionnaire was utilized to conduct an Australian study published by Dulhunty et al.[14] and is composed of fictitious clinical cases of patients with severe infection. In the present study, only cases of respiratory infection were analyzed: community-acquired pneumonia and nosocomial pneumonia. Both settings are described in the electronic supplementary materials.

All participants were asked to indicate their medical specialty, their years of experience in the ICU and the characteristics of the hospital/ICU at which they worked. In addition, for each clinical case, they were requested to indicate how many and which antibiotics they would prescribe, their dose and duration. For these cases, the presence of empyema or any other complication that required surgical intervention or an invasive procedure was discarded. The weight of the patient was indicated as being 80kg, and their renal and liver function was listed as normal.

They were asked to choose between one and three antibiotics without including antivirals, antifungals or tuberculostatic drugs. The dose of medication was calculated and expressed in g per day.

The two settings were bilateral community-acquired pneumonia with secondary septic shock (case 1, available in the electronic supplementary materials); and nosocomial pneumonia in the postoperative period following cholecystectomy (case 2, available in the electronic supplementary materials).

The number of antibiotics indicated, along with their dose and duration, was recorded. The indicated regimen and the dose of antibiotic were then consulted according to the indications from the respective therapeutic guides. As specific indications for Latin America did not exist, we decided to utilize the IDSA/ATS recommendations.[9,10] In table S1 of the electronic supplementary materials, the recommended antibiotic regimens are indicated. In the case of prescription of antibiotics that were not indicated in the recommendations or where the dose of antibiotic established by the IDSA/ATS was omitted, the dose suggested by the manuals with the greatest frequency of clinical use was considered to be valid.[15]

Because this was a spontaneous survey conducted using fictitious clinical cases, informed consent was not solicited to perform this study. The survey participants were informed about the purpose of the survey and notified that their compliance was not a condition for obtaining the certificate of course participation.

The results are expressed as the medians and interquartile ranges for continuous variables or as an absolute frequency and percentage frequency for categorical variables. The data management and the statistical analysis were conducted using Statistical Package for the Social Sciences (SPSS) version 15.

RESULTS

Thirty-six physicians responded to the survey: 56% (20 physicians) were ICU specialists with > 5 years of experience in the ICU; 33% (12) were specialists in infectious diseases; and 3% (1) were ICU specialists with < 5 years of experience. Less than 10% (3 physicians) identified with another specialty: anesthesia, internal medicine or cardiology (Table 1). Seventeen physicians (47%) worked in an academic institution; 31 of 36 (86%) practiced in a medical-surgical ICU. The provenance was primarily from Brazil (25 physicians; 69%), followed by Venezuela (4; 11%), Mexico (2; 6%) and Chile (2; 6%).

In the two clinical cases, a total of 135 antibiotics were detailed (Tables 2 and 3): 68 in the first case and 67 in the second. In case 1, the most employed group of antibiotics was beta-lactams (29 of 68 prescriptions; 42.7%), with ceftriaxone being prescribed in 29.4% of cases. Macrolides (clarithromycin and azithromycin) were indicated in 19 of 68 prescriptions (27.9%), and quinolones (levofloxacin and moxifloxacin) were indicated in 8 (11.8%). The most prescribed antibiotic patterns were as follows (Figure 1): ceftriaxone and clarithromycin (9 patients of 36; 25.0%),

Table 1 - Information from the 36 survey participants

	Frequency
Specialization	
Intensive care for more than 5 years	20 (55.6)
Intensive care for less than 5 years	1 (2.8)
Infectious diseases	12 (33.3)
Other specialties	3 (8.3)
Type of hospital	
University	17 (47.2)
Non-university	5 (13.9)
Did not answer	14 (38.9)
Hospital funding	
Public	18 (50.0)
Private	11 (30.6)
Did not answer	7 (19.4)
Type of ICU	
Mixed medical-surgical	31 (86.1)
Medical	2 (5.6)
Surgical	0
Did not answer	3 (8.3)
Level of care	
Third level	27 (75.0)
Second level	1 (2.8)
Did not answer	8 (22.2)
Participant origin	
Brazil	25 (69.4)
Venezuela	4 (11.1)
Mexico	2 (5.6)
Chile	2 (5.6)
Did not answer	3 (8.3)

Results are expressed as the absolute values and percentages: n (%). ICU - intensive care unit.

ceftriaxone/cefotaxime and azithromycin (5 patients; 13.9%), and ceftriaxone and levofloxacin/moxifloxacin (5; 13.9%). In 32 of 36 cases (88.9%), combined treatment was indicated. Active anti-*Pseudomonas* treatment was prescribed in 15 of 36 patients (41.7%) while treatment for methicillin-resistant *Staphylococcus aureus* (MRSA) was indicated in 6 of 36 patients (16.7%).

Treatment was adequate according to the IDSA/ATS recommendations in 11 of 36 prescriptions (30.6%) (Table 4). The causes of non-compliance were monotherapy (4 of 25; 16.0%); unnecessary coverage for *P. aeruginosa*/MRSA in 10 prescriptions (40.0%); and administration of double antibiotic treatment with medications that were not indicated in 11 of 25 prescriptions (44.0%). The most employed antibiotics were clarithromycin (10 prescriptions), clindamycin (1 prescription) and amoxicillin clavulanic (1 prescription).

In case 2, the most indicated antibiotics were meropenem (20 prescriptions of 67; 29.9%), vancomycin (14; 20.9%), linezolid (14; 20.9%) and piperacillin-tazobactam (13; 19.4%) (Table 3). The most highly employed regimens are shown in figure 2: meropenem and linezolid (10 patients of 36; 27.8%), meropenem and vancomycin (9 patients of 36; 25.0%), piperacillin-tazobactam and linezolid (5 of 36; 13.9%) and piperacillin-tazobactam in monotherapy (5; 13.9%). Monotherapy was indicated in 5 of 36 patients (13.9%), and combined antibiotic treatment was prescribed in the 31 remaining patients (86.1%). In all cases, active treatment was indicated for *P. aeruginosa*. Active treatment for MRSA was indicated in 30 of 36 patients (83.3%).

Table 2 - Antibiotic prescription, dose and duration in the case of community-acquired pneumonia

Antibiotic	N indications	Dose*	Indicated dose ≥ recommendation	Duration < 7 days	Duration 7 - 10 days	Duration > 10 days
Beta-lactams	29/68 (42.7)					
Ceftriaxone	20/68 (29.4)	2.0 (2.0 - 3.5)	19/20 (95.0)	0/20 (0)	17/20 (85.0)	3/20 (15.0)
Cefepime	5/68 (7.4)	6.0 (5.0 - 6.0)	4/5 (80.0)	0/5 (0)	3/5 (60.0)	2/5 (40.0)
Meropenem	4/68 (5.9)	3.0 (1.9 - 3.0)	3/4 (75.0)	0/4 (0)	3/4 (75.0)	1/4 (25.0)
Macrolides	19/68 (27.9)					
Clarithromycin	10/68 (14.7)	1.0 (0.9 - 1.0)	8/10 (80.0)	0/10 (0)	8/10 (80.0)	2/10 (20.0)
Azithromycin	9/68 (13.2)	0.5 (0.5 - 1.0)	9/9 (100)	0/9 (0)	7/9 (77.8)	2/9 (22.2)
Quinolones	8/68 (11.8)					
Levofloxacin	4/68 (5.9)	0.8 (0.6 - 0.8)	3/4 (75.0)	0/4 (0)	4/4 (100)	0/4 (0)
Moxifloxacin	4/68 (5.9)	0.4 (0.4 - 1.3)	4/4 (100)	0/4 (0)	4/4 (100)	0/4 (0)
Glycopeptides	4/68 (5.9)					
Vancomycin	4/68 (5.9)	2.0 (2.0 - 2.0)	4/4 (100)	0/4 (0)	3/4 (75.0)	1/4 (25.0)
Others	8/68 (11.8)					

Results are expressed as the absolute values and percentages: n (%); * result is expressed as the median and interquartile range.

Table 3 - Antibiotic prescription, dose and duration in the case of nosocomial pneumonia

Antibiotic	N indications	Dose*	Indicated dose ≥ recommendation	Duration < 7 days	Duration 7 - 10 days	Duration > 10 days
Beta-lactams	33/67 (49.3)					
Meropenem	20/67 (29.9)	3.0 (3.0 - 6.0)	18/20 (90.0)	0/20 (0)	13/20 (65.0)	7/20 (35.0)
Piperacillin-tazobactam	13/67 (19.4)	18.0 (15.8 - 18.0)	12/13 (92.3)	0/13 (0)	10/13 (76.9)	3/13 (23.1)
Glycopeptides	14/67 (20.9)					
Vancomycin	14/67 (20.9)	2.0 (2.0 - 2.0)	14/14 (100)	0/14 (0)	12/14 (85.7)	2/14 (14.3)
Oxazolidinones	14/67 (20.9)					
Linezolid	14/67 (20.9)	1.2 (1.2 - 1.2)	14/14 (100)	0/14 (0)	9/14 (64.3)	5/14 (35.7)
Others	6/67 (8.9)					

Results are expressed as the absolute values and percentages: n (%); * result is expressed as the median and interquartile range.

Table 4 - Fulfillment of Infectious Disease Society of America/American Thoracic Society recommendations and reasons for non-adherence

Clinical case	Adherence to recommendations		Case 1 - Reasons for non-adherence			Case 2 - Reasons for non-adherence	
	Complied	Not complied	Monotherapy	multiR coverage	Non-indicated AB	Monotherapy	Without double PA coverage
Community-acquired pneumonia Case 1	11/36 (30.6)	25/36 (69.4)	4/25 (16.0)	10/25 (40.0)	11/25 (44.0)		---
Nosocomial pneumonia Case 2	1/36 (2.8)	35/36 (97.2)		---		5/35 (14.3)	30/35 (85.7)

Results are expressed as the absolute values and percentages: n (%). multiR - multi-resistant; AB - antibiotic; PA - *Pseudomonas aeruginosa*.

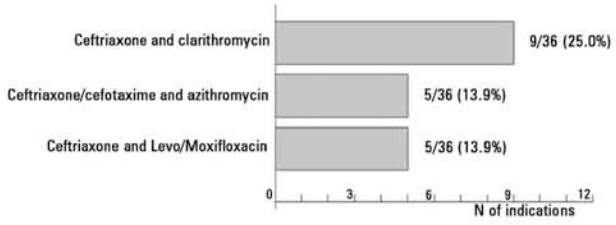

Figure 1 - Antibiotic regimens most frequently indicated in the case of community-acquired pneumonia.

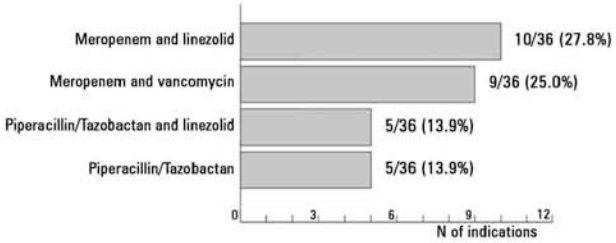

Figure 2 - Antibiotic regimens most frequently indicated in the case of nosocomial pneumonia.

Adherence to the IDSA/ATS indications occurred in 3% of patients (1 patient of 36, with meropenem and levofloxacin being indicated) (Table 4). The causes of non-compliance were monotherapy in 5 prescriptions of 35 (14.3%) and lack of double antibiotic coverage for *P. aeruginosa* in 30 indications of 35 (85.7%). If the administration of only one active antibiotic for *P. aeruginosa* had been considered adequate, as indicated in other recommendations,[16] whether it was paired with an active antibiotic for MRSA, the rate of appropriate treatment would have been 100%.

DISCUSSION

The most noteworthy conclusion from this study population is the limited adherence to IDSA/ATS recommendations when prescribing empirical antibiotics for severe pneumonia. In line with the results obtained from studies conducted on other continents,[11-14] this conclusion carries strong implications because a low adherence to therapeutic recommendations is associated with greater morbidity and mortality as well as with an increase in health costs.[4,8,17]

Studies conducted in Europe report adherence rates of between 20 and 100%. The proposed causes of non-adherence were differences between the patient being treated and the condition described in the guidelines, the presence of kidney or liver failure, the unavailability or excessive costs of specific antibiotics, and differences between local flora and international recommendations.[11,12,18]

In the case of community-acquired pneumonia, treatment was adequate in 31% of patients (11 of 36). Although the therapeutic guidelines recommend initiation

of broad-spectrum treatment in high-suspect cases of multi-resistant pathogens, this was not considered a correct option because in the setting presented, the patient did not have risk factors for nosocomial pathogens. There were various causes of non-adherence. Prescription of monotherapy (16%) was a reason for non-adherence, as various studies have shown that in patients with respiratory shock, combination antibiotic treatment reduces mortality.[19-21] In addition, a clinical trial conducted in patients with severe community-acquired pneumonia concluded that mortality is higher in patients who received fluoroquinolone versus bitherapy, although statistical significance was not achieved.[22] In general, every patient admitted to the ICU with severe CAP should receive treatment for pneumococcus and *Legionella pneumophila*, using an anti-pneumococcal bactericide, with the first option being a beta-lactam and an active agent for *Legionella* spp., such as levofloxacin or azithromycin.[23,24]

Another cause for the lack of adherence was the extensive coverage for *P. aeruginosa* and MRSA. A total of 40% of patients received active multi-resistant treatment. It has been previously shown that the prevalence of multi-resistant organisms and MRSA is higher in Latin America than in other countries.[25,26] However, the extensive use of broad-spectrum antibiotics leads to an increase in the appearance of opportunistic pathogens.[27-29] Because of this fact, it is essential to monitor the local bacterial flora.[9]

The third reason for the lack of adherence was the prescription of antibiotics not indicated in the recommendations. A total of 44% of patients received treatment with a non-antipseudomonal cephalosporin in addition to clarithromycin. In the 2003 IDSA guidelines, the association of a beta-lactam with a macrolide (erythromycin, clarithromycin or azithromycin) is indicated,[30] while in the latest update,[9] azithromycin is recommended.

The utility of macrolides has been essential in the treatment of pneumonia, due to their activity against pneumococcus and atypical pathogens.[31] The utility of erythromycin, the first macrolide available, has diminished due to its gastrointestinal adverse effects, lack of efficacy against *Haemophilus influenzae* and the emergence of pneumococcus resistance.

The main advantages of azithromycin and clarithromycin compared to erythromycin are less adverse effects and greater tissue penetration, stability against gastric pH, greater half-life, few pharmacological interactions and a greater post-antibiotic effect. The tissue concentration of azithromycin can be between 10 and 100 times greater than that obtained in blood.[32] Although the maximum concentrations reached by azithromycin and clarithromycin are close to the maximum values of the minimum inhibitory concentration for the important pathogens, their rapid collection in the intra-cellular compartment and their slow liberation make them efficient for this purpose. This phenomenon is more marked with azithromycin due to a more prolonged antimicrobial exposure as a result of its post-antibiotic effect, which allows 3-5-day treatment cycles to be sufficient.[33] However, a limitation of azithromycin is its high intra-cell/interstitial concentration quotient, which could justify its bad behavior against extracellular microorganisms.[34]

In the case of nosocomial pneumonia, an adherence of only 3% of the recommendations is noteworthy, with the only adequate regimen being meropenem and levofloxacin. The IDSA/ATS recommendations indicate using a beta-lactam paired with an aminoglycoside or an active quinolone for *P. aeruginosa*. In the case of MRSA infection risk, its coverage is indicated. However, in the present case, it was not considered necessary to provide coverage for MRSA, although providing coverage for this infection was not classified as inadequate.

Of the 35 inadequate regimens, monotherapy was indicated in five cases, always ensuring *Pseudomonas aeruginosa* coverage; on the other hand, combined therapy was indicated in 30 cases. In all the 30 cases of combined therapy, at least one antibiotic was active against *P. aeruginosa* and another was active against MRSA. The IDSA/ATS recommendations suggest initiating a double antipseudomonal treatment with the purpose of minimizing the risk of not covering the pathogen due to an antibiotic resistance pattern.

Garnacho-Montero et al. addressed monotherapy versus bitherapy in ventilator-associated pneumonia due to *P. aeruginosa*. In their conclusions, they confirm that combination treatment reduces the risk of inadequate empirical treatment. However, there were no differences in mortality between monotherapy and combination therapy. In addition, the cases of *Pseudomonas* with reduced sensitivity to carbapenems that received 6g of meropenem per day did not increase mortality.[35] In this sense, in a hospital institution at which the resistance of *P. aeruginosa* to carbapenem is not a problem, the use of monotherapy with high-dose of meropenem could be an acceptable option. Similarly, the utilization of a beta-lactam in monotherapy in an environment with very low risk of antibiotic resistance could be an adequate option. Despite this, the lack of randomized clinical trials does not allow this finding to be generalized. To support this assertion, according to the European recommendations,[16] a patient with nosocomial pneumonia that is acquired within the first four days of admittance should receive only one antibiotic. Considering

the administration of an anti *P. aeruginosa* to be adequate in our population, the rate of adherence would be 100%.

The present analysis has several limitations. Most importantly, this is a clinical survey based on fictitious cases, and therefore, the data do not come from real clinical practice. However, the high rate of intensive care physicians or infectious disease specialists with extensive work experience in the ICU in a third-level university setting confers a high validity and reliability to the study results.

Another important limitation is that the majority of those surveyed came from Brazil, and there was not, therefore, a proportional representation of the different Latin American countries. An analysis was conducted to compare the responses of physicians from and not from Brazil, and no significant differences were obtained. In addition, the physicians came from different cities in Brazil and from other Latin American countries. Due to confidentiality considerations and to not bias the responses, the authors decided not to communicate the survey participants' cities of origin. Finally, a higher number of survey participants may have supplied more representative data. The conduction of a similar study with a greater sample size could be useful for confirming the findings obtained and guaranteeing a higher reproducibility and representation of all Latin American states.

CONCLUSION

In the present survey on empirical antibiotic prescription in severe pneumonia, which was conducted using a small sample of physicians from Latin America, adherence to therapeutic Infectious Disease Society of America/American Thoracic Society guidelines was relatively low. However, these findings were in line with results from studies conducted on other continents. In the case of community-acquired pneumonia, the causes of non-adherence were the high indication of monotherapy, coverage for multi-resistant pathogens made when it was not indicated and the employment of antibiotics that were not indicated. In the case of nosocomial pneumonia, the most important cause of non-compliance was the use of only one active antibiotic for *P. aeruginosa*.

RESUMEN

Objetivo: Valorar tasa de adherencia y causas de no adherencia a las guías terapéuticas internacionales para la prescripción antibiótica empírica en la neumonía grave en Latinoamérica.

Métodos: Encuesta clínica realizada a 36 médicos de Latinoamérica donde se pedía indicar el tratamiento empírico en 2 casos clínicos ficticios de pacientes con infección respiratoria grave: neumonía adquirida en la comunidad y neumonía nosocomial.

Resultados: En el caso de la neumonía comunitaria el tratamiento fue adecuado en el 30,6% de las prescripciones. Las causas de no adherencia fueron monoterapia (16,0%), cobertura no indicada para multirresistentes (4,0%) y empleo de antibióticos con espectro inadecuado (44,0%). En el caso de la neumonía nosocomial el cumplimiento de las guías terapéuticas *Infectious Disease Society of America/American Thoracic Society* fue del 2,8%. Las causas de falta de adherencia fueron monoterapia (14,3%) y la falta de doble tratamiento antibiótico frente a *Pseudomonas aeruginosa* (85,7%). En caso de considerar correcta la monoterapia con actividad frente a *P. aeruginosa*, el tratamiento sería adecuado en el 100% de los casos.

Conclusión: En la neumonía comunitaria la adherencia a las guías terapéuticas *Infectious Disease Society of America/American Thoracic Society* fue del 30,6%; la causa más frecuente de incumplimiento fue el uso de monoterapia. La adherencia en el caso de la neumonía nosocomial fue del 2,8% y la causa más importante de incumplimiento fue la falta de doble tratamiento frente a *P. aeruginosa*, considerando adecuada monoterapia con actividad frente a *P. aeruginosa* la adherencia sería del 100%.

Descriptores: Infecciones comunitarias adquiridas/quimioterapia; Neumonía asociada al ventilador/quimioterapia; Antibacterianos/uso terapéutico; Adhesión a las directivas anticipadas

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What Is New in Antibiotic Therapy in Community-Acquired Pneumonia? An Evidence-Based Approach Focusing on Combined Therapy

Simone Gattarello[1]

Abstract Despite all published literature, controversies remain about the optimal antibiotic treatment in community-acquired pneumonia. The most debated issue is whether it is necessary to empirically start one or two antibiotics, i.e. whether or not to cover atypical agents. A review of the literature published from 2005 to present was completed, searching for new insights in antibiotic treatment in community-acquired pneumonia (CAP) focusing on monotherapy versus combined therapy. Forty-one articles were identified enrolling outpatients, and patients admitted to the ward and to the intensive care unit: 11 were meta-analyses, 8 clinical trials and 22 observational—prospective and retrospective—studies. Although controversies remain in the treatment of CAP, the use of combination therapy seems to be associated with a lower mortality in case of severe CAP that requires intensive care unit (ICU) admission, especially when a beta-lactam–macrolide association is delivered. Moreover, combination therapy is associated with better outcomes—although not always with a lower mortality—in cases of non-ICU patients with risk factors for a poor outcome, bacteraemic pneumococcal pneumonia and high suspicion of infection by atypical agents. In this setting, it appears that the best choice of treatment may be a beta-lactam–macrolide regimen.

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Keywords Community-acquired pneumonia · Antibiotic treatment · Monotherapy · Combined therapy · Guidelines

Abbreviations

CAP	Community-acquired pneumonia
ICU	intensive care unit
PSI	Pneumonia severity index

Introduction

Community-acquired pneumonia (CAP) is a common and potentially severe disease. In Europe, it is estimated that the annual incidence in younger adults is 1.2 cases per 1000 person-years, increasing up to 14 per 1000 in patients over 65 years old [1].

In Western countries, mortality due to CAP varies widely depending from the severity of the illness: less than 1 % in individuals treated outside the hospital; around 10 % in hospitalised non-intensive care unit (ICU) patients, and up to 20 to 40 % in severe forms, i.e. when ICU admission is required [2, 3•].

In CAP, antibiotic therapy is the cornerstone of treatment; after diagnosis of pneumonia is done, an adequate antimicrobial therapy is always recommended, as it has been associated with better outcomes [4, 5]. Adequate antibiotic therapy is defined as the treatment that covers all suspected pathogens, and it is usually started on the basis of epidemiological and clinic considerations as well as local guidelines [4]. Although CAP may be caused by many pathogens, a reduced number of microorganisms are responsible for the majority of cases; classically, they are classified into typical and atypical.

Guidelines for the management of CAP were published [4, 6], and the antibiotic regimens proposed are classified

according with the site of care: outpatients, ward or intensive care unit (ICU).

What Do the Guidelines Recommend?

Outpatients

In outpatients with CAP, the Infectious Diseases Society of America/American Thoracic Society (IDSA/ATS) guidelines recommend administration of a macrolide (azithromycin, clarithromycin or erythromycin) or doxycycline. If a patient received antibiotic therapy within 3 previous months, or presents with some risk factor for a higher mortality for CAP (chronic heart disease, lung or liver disease, diabetes mellitus, alcohol abuse, malignancy, asplenia or hyposplenism, immunocompromised status), the recommended antibiotic regimen is a respiratory fluoroquinolone (moxifloxacin, gemifloxacin or high-dose levofloxacin), or a combination of a beta-lactam (high-dose amoxicillin or amoxicillin–clavulanate, ceftriaxone, cefuroxime or cefpodoxime) with a macrolide. In the same setting, European guidelines recommend the administration of amoxicillin or a tetracycline. If these agents are considered contraindicated or there is a high suspicion of infection by atypical agents, the indication is monotherapy with a macrolide or a respiratory fluoroquinolone. Both American and European guidelines suggest considering the local flora pattern of antibiotic resistance.

Ward

In the case of patients with CAP who require hospitalisation, the IDSA/ATS guidelines suggest administration of a respiratory fluoroquinolone, and a beta-lactam (cefotaxime, ceftriaxone, ampicillin or ertapenem) plus a macrolide or doxycycline if patients have a high risk of pneumonia due to Gram-negative bacilli. As stated in the guidelines, monotherapy with a macrolide should be avoided because of the high rate of macrolide-resistant pneumococci. In the same setting, European guidelines suggest the administration of an aminopenicillin with or without a beta-lactamase inhibitor or a cephalosporin (ceftriaxone or cefotaxime), and to consider the addition of azithromycin or clarithromycin. In the case of high suspicion for *Streptococcus pneumoniae*, as several publications have demonstrated that low-level resistance to penicillin is not associated with worsened outcomes [7], penicillin G plus a macrolide could be an alternative. If those antibiotics are considered inappropriate, a respiratory fluoroquinolone may be an alternative. As stated in the European guidelines, the use of a specific antibiotic pattern should be guided by the severity of the disease (most severe cases should be treated with combined therapy) and based on considerations of allergy, intolerance, previous use of penicillins, macrolides or fluoroquinolones, cost and potential adverse effects.

Intensive Care Unit

According to both the American and the European guidelines, a patient in an ICU setting should be covered for all suspected microorganisms (resistant *Streptococcus pneumoniae* and atypical pathogens) because it was observed in severe CAP that an inadequate antibiotic treatment is associated with an increased mortality [8].

IDSA/ATS guidelines suggest initiating a combination regimen with a beta-lactam (cefotaxime, ceftriaxone or ampicillin–sulbactam) plus either azithromycin or a respiratory fluoroquinolone. Likewise, European guidelines suggest combination therapy in the form of a non-antipseudomonal third-generation cephalosporin (ceftriaxone or cefotaxime) plus either a macrolide (azithromycin or clarithromycin) or a respiratory fluoroquinolone. Both guidelines recommend that if an infection by methicillin-resistant *Staphylococcus aureus* or *Pseudomonas aeruginosa* is suspected, the antibiotic treatment should empirically cover these microorganisms. Conversely, it was demonstrated that the regular coverage of resistant agents did not decreased mortality [9].

Controversies regarding the optimal antibiotic regimen persist; the most debated issues are whether it is necessary to empirically cover atypical microorganisms, and if it is better to start one antibiotic or two. In the present review, all articles aimed at the study of monotherapy versus combination therapy in CAP were reviewed.

Material and Methods

A review of the literature was performed searching for any recent article about antibiotic treatment in CAP. The search process was performed in PubMed in March 2015; articles in English, performed in adults and published from January 1, 2005 to March 1, 2015, were selected. The search key was "community-acquired pneumonia" plus "antibiotic".

Of all the studies individuated, the ones that assessed differences in outcomes after the administration of different antibiotic regimens were selected; finally, the articles that compared monotherapy versus combination therapy or compared different patterns of combination therapy were chosen for the present review. Publications on health-care-associated pneumonia and aspiration pneumonia were excluded from the analysis. The items found in the review were then analysed and classified as meta-analysis, clinical trial or observational study.

Those articles that included either outpatients and patients proceeding from the ward were categorized in the present review as outpatients. Likewise, articles enrolling both patients from the ward and ICU patients were categorized in the present review as ward-patients.

Results

The PubMed search obtained 2233 results. The screen resulted in a total of 41 selected articles: 11 meta-analyses, 8 clinical trials and 22 observational—prospective and retrospective—studies.

What Is New in the Literature?

Since 2005, several studies were published assessing monotherapy versus combination therapy in CAP.

Outpatients

Four papers were identified: three meta-analyses and one observational study (Table 1).

The most recent article is a Cochrane meta-analysis published in 2014 by Pakhale et al. [10] that explored changes in mortality by using different antibiotic prescriptions—in monotherapy and combined therapy—in outpatients with CAP: 11 clinical trials were included without observing differences in mortality or in the incidence of adverse effects. A meta-analysis by Skalsky et al. [11] included 16 trials enrolling both outpatients and ward patients exploring whether the administration of a macrolide-based versus fluoroquinolone-based regimen was associated with different outcomes. As a conclusion, no differences were observed in all-cause mortality between the two regimens of antibiotics. Treatment failure and microbiological failure decreased significantly when a fluoroquinolone was administered, and a higher incidence of adverse event and antibiotic discontinuation was associated with macrolide prescription, mainly attributed to digestive complications. Thus, although these finding were not associated with changes in mortality, authors conclude that fluoroquinolones may be superior when compared with macrolides.

Finally, An et al. in 2010 published a meta-analysis [12] comparing outcomes after administration of moxifloxacin versus a beta-lactam-based combination with a macrolide. Seven trials were identified including around 4000 patients. Again, no differences were observed regarding mortality, clinical success and adverse effects rates. Conversely, microbiological failure was significantly lower with moxifloxacin.

One observational study by Ye et al. [13] compared outcome and costs of treatment in outpatients with CAP after administration of levofloxacin (500 or 750 mg) versus macrolides: Although the rate of treatment failure was lower for the levofloxacin group, no differences were observed in term of costs, CAP-related hospitalisations and mortality.

Ward

Twenty-seven articles were identified: 7 meta-analyses (Table 2), 7 clinical trials (Table 3) and 13 observational studies (Table 4).

A Cochrane meta-analysis by Eliakim-Raz et al. [16] explored changes in mortality depending on coverage for atypical agents; 28 clinical trials were included, and no difference in mortality or in the development of adverse effects was observed. Patients who received atypical coverage showed a non-significant trend toward clinical and microbiological resolution. This trend was statistically significant in patients with

Table 1 Published studies in outpatients that assess monotherapy versus combination therapy

Author	Year	Study design	Study population	Objective	Outcomes
Pakhale et al. [10]	2014	Meta-Analysis	11 RCTs	Compare efficacy and safety of different antibiotic regimens in CAP	Same mortality and clinical success rate between different antibiotic regimens
Skalsky et al.[a] [11]	2013	Meta-Analysis	16 RCTs, mostly in outpatients with mild to moderate CAP	Compare outcomes after mono or combined therapy with macrolide or quinolone regimens	No differences in mortality; higher eradication rate with quinolones; macrolides associated with higher adverse effects
An et al. [12]	2010	Meta-Analysis	7 RCTs	Compare efficacy and safety of moxifloxacin monotherapy versus BL regimens	No difference in mortality, clinical resolution or adverse effects; quinolones had higher eradication rate
Ye et al. [13]	2008	Observational	Retrospective, enrolling 7526 patients	Compare treatment failure, safety, outcomes and costs of levofloxacin (500 and 750 mg) versus macrolides	Levofloxacin associated with lower treatment failure, especially in over 65. No differences in hospitalization or costs of treatment

CAP community-acquired pneumonia, *RCT* randomized controlled trial, *BL* beta-lactam

[a] The study includes outpatients and ward patients

Table 2 Published meta-analyses in ward patients that assess monotherapy versus combination therapy

Author	Year	Study population	Objective	Outcomes
Nie et al.[a] [14]	2014	16 observational studies: 4 prospective and 12 retrospectives	Compare mortality after BL monotherapy versus BL–macrolide combination therapy	Mortality was higher in patients receiving monotherapy
Zhang et al. [15]	2013	10 RCTs: 5 compared gemifloxacin with quinolones, and 5 gemifloxacin versus BL and/or macrolides	Compare mortality and efficacy of gemifloxacin versus other approved regimens	Comparable mortality, treatment and microbiological failure rate were observed
Eliakim-Raz et al. [16]	2012	28 RCTs	Compare mortality and adverse effects after empirical coverage or not of atypical agents	Same mortality and adverse effects after coverage or not of atypical agents; in case of *Legionella* infection higher clinical resolution after atypical coverage
Yuan et al. [17]	2012	14 RCTs	Compare outcomes after moxifloxacin monotherapy versus other approved regimens	Same mortality and adverse effects; moxifloxacin was associated with higher eradication rate
Asadi et al. [18]	2012	23 either RCTs and observational studies, including 137,574 patients	Compare outcomes between macrolides versus other approved regimens	Lower mortality with macrolides; same mortality when only RCTs were analysed
Varner et al. [19]	2011	4 bioactivity evaluations, 6 clinical studies and 6 reported cases of combination rifampin use	Compare mortality after addition of rifampicin in *Legionella* pneumonia	Scarce data available; consider rifampicin addition only in severe or refractory pneumonia and presence of risk factors
Vardakas et al. [20]	2008	23 RCTs	Compare outcomes between quinolone versus BL with/without macrolides	Same mortality, although higher success of treatment with quinolones

BL beta-lactam, *RCT* randomized controlled trial

[a] The study includes ward and ICU patients

pneumonia due to *Legionella pneumophila*, still without observing changes in mortality.

Two meta-analyses found a decreased mortality after addition of a macrolide to the treatment; Nie et al. [14] compared a beta-lactam–macrolide regimen versus beta-lactam monotherapy in a meta-analysis that only included observational studies enrolling ward and ICU patients. In the conclusions, combined therapy resulted in a significant decrease of mortality. Likewise, Asadi et al. [18] in a meta-analysis that included 23 studies of in-hospital patients with CAP—either clinical trials or observational studies—observed a significant reduction of mortality in individuals who received a macrolide regimen. Importantly, this trend was not significant when only the clinical trials were analysed, or in patients who received guideline-concordant antibiotics.

Three meta-analyses compared outcomes after administration of a respiratory fluoroquinolone versus a beta-lactam regimen. After comparing oral gemifloxacin with a beta-lactam regimen in mild to moderately severe patients with CAP and bronchial exacerbations, Zhang et al. [15] observed a comparable mortality between the two arms. Gemifloxacin was associated with a higher rate of adverse effects, mostly in form of gastrointestinal complications. Two other meta-analyses in 2008 and 2012 achieved similar conclusions; Vardakas et al. [20] compared the use of monotherapy with fluoroquinolones versus a combination beta-lactam regimen documenting a comparable mortality, although a higher eradication rate after fluoroquinolone administration was observed. Yuan et al. [17] observed a comparable mortality and a higher rate of microbial eradication after administration of moxifloxacin versus a beta-lactam antibiotic regimen.

Finally, a meta-analysis by Varner et al. [19] explored the benefit of the addition of rifampicin to the standard treatment of CAP due to *L. pneumophila*, without observing different outcomes. Authors concluded that rifampicin should not be added to treat CAP due to *Legionella* spp. unless pneumonia is severe or is refractory to the standard treatment.

In the last years, several clinical trials were published assessing outcomes after comparing monotherapy versus combination therapy. In a recent study, Postma et al. [21] did not find differences in mortality after comparing fluoroquinolone monotherapy versus beta-lactam monotherapy versus beta-lactam–macrolide combination in non-ICU hospitalised patients; thus, authors concluded that beta-lactam monotherapy was non-inferior to other regimens. Garin et al. [22] obtained similar conclusions: No differences in mortality, length of stay and ICU admission were observed after administration of a beta-lactam alone versus a beta-lactam–macrolide regimen.

Table 3 Published clinical trials in ward patients that assess monotherapy versus combination therapy

Author	Year	Study population	Objective	Outcomes
Postma et al. [21]	2015	Multicentric, cluster-randomized clinical trial, enrolling 2283 patients	Compare outcomes after BL alone, quinolone alone or BL–macrolide combination	Comparable mortality between different antibiotic regimens
Garin et al. [22]	2014	Non-inferiority, multicentric, randomized clinical trial, in 580 patients	Compare clinical outcomes after BL alone versus BL–macrolide association	Comparable mortality, length of stay and recurrence of pneumonia. Delayed clinical stability after monotherapy in atypical pneumonia and PSI V pneumonias
Lee et al. [23]	2012	Open-label, unicentric, randomized clinical trial, enrolling 40 patients	Compare outcome after high-dose levofloxacin or ceftriaxone plus azithromycin	Levofloxacin 750 mg per day showed same mortality, clinical success and microbiological eradication rate than ceftriaxone plus azithromycin
Torres et al.[a] [24]	2008	Multicentric, randomized, double-blind non-inferiority trial, enrolling 733 patients with PSI score III to V	Compare outcomes after moxifloxacin monotherapy versus ceftriaxone plus levofloxacin	Comparable mortality, adverse effects, clinical success and eradication rate between the 2 arms
Lin et al. [25]	2007	Open-label, randomized, unicentric clinical trial, enrolling 50 patients	Compare outcomes after levofloxacin versus amoxicillin-clavulanate plus clarithromycin	Comparable mortality and clinical success rate were observed
Xu et al. [26]	2006	Unicentric, randomized, open-label clinical trial, enrolling 40 patients	Compare outcomes after moxifloxacin versus cefoperazone plus azithromycin	No differences were observed in terms of mortality, microbiological eradication and adverse effects
Portier et al. [27]	2005	Multicentric, randomized, open-label clinical trial, enrolling 346 patients	Compare outcomes between moxifloxacin versus amoxicillin-clavulanate plus roxithromycin in CAP with risk factors	No differences in mortality, eradication rate or adverse effects

BL beta-lactam, *RCT* randomized controlled trial, *CAP* community-acquired pneumonia, *PSI* pneumonia severity index

[a] The study includes ward and ICU patients

Patients with a pneumonia severity index (PSI) score of IV or V and patients infected by atypical microorganisms presented delayed clinical stability with monotherapy. Other studies documented similar conclusions; a comparable mortality and adverse effect rates, and a higher eradication rate in the fluoroquinolone group were observed by Lee et al. [23] after comparing high-dose levofloxacin versus ceftriaxone plus azithromycin. No differences in mortality or an increased eradication rate in the fluoroquinolone arm were found when comparing a fluoroquinolone versus a beta-lactam plus a macrolide [25–27]. One clinical trial by Torres et al. [24] did not observe differences in mortality after comparing moxifloxacin monotherapy with ceftriaxone plus levofloxacin in a cohort of CAP patients including 10 % with severe pneumonia (PSI score IV or V).

Thirteen observational studies were identified. Several studies, either prospective or retrospective, compared fluoroquinolone monotherapy with a beta-lactam monotherapy regimen. Asadi et al. [28] did not find a difference in mortality after comparing fluoroquinolone monotherapy with a beta-lactam–macrolide regimen, in ward and ICU patients. When comparing high-dose levofloxacin with ceftriaxone plus azithromycin, a similar mortality was observed, but a decrease in costs of treatment was documented after fluoroquinolone administration [30, 33–35, 38, 39].

A decreased mortality was observed after the administration of a beta-lactam–macrolide combination when compared with beta-lactam monotherapy [29, 32, 40]. In the paper by Rodrigo et al., these conclusions were not observed in the mildest forms of CAP. On the other hand, in patients with severe CAP with pneumococcal bacteraemia, a difference in mortality was not found between the administration of a beta-lactam plus a macrolide and monotherapy with a beta-lactam [37].

Two observational studies explored changes in mortality after the addition of a macrolide. Restrepo et al. [31] found that patients with CAP and severe sepsis had a decreased mortality when a macrolide was added. Metersky et al. [36] achieved the same conclusions in patients with bacteraemic CAP admitted to the ward or in the ICU.

Intensive Care Unit

Ten studies were identified: one meta-analysis, one clinical trial and eight observational studies (Table 5).

In 2014, Sligl et al. [41] published a meta-analysis exploring outcomes after administration of combined therapy with a macrolide regimen versus monotherapy or combined therapy without a macrolide; 28 observational studies enrolling critically ill patients with CAP were included, accounting for nearly 10,000 patients. As a conclusion, mortality was lower in

Table 4 Observational studies published in ward patients that assess monotherapy versus combination therapy

Author	Year	Study population	Objective	Outcomes
Asadi et al.[a] [28]	2013	Multicentric, retrospective, enrolling 3203 patients, 63 % of which with PSI score IV/V	Compare outcomes after BL–macrolide versus quinolone	No differences in mortality between different regimens
Rodrigo et al.[a] [29]	2013	Multicentric, retrospective, enrolling 5240 patients	Compare mortality after BL–macrolide versus BL alone in CAP depending from severity	Higher mortality in moderate and severe CAP while comparable mortality was observed in milder forms
Frei et al. [30]	2009	Multicentric, retrospective enrolling 495 patients	Compare length of stay and antibiotic duration after administration of high dose levofloxacin versus ceftriaxone plus azithromycin	Lower length of stay and length of treatment were observed after high dose levofloxacin
Restrepo et al.[a] [31]	2009	Multicentric, retrospective, enrolling 237 patients	Explore changes in mortality after addition of a macrolide in CAP with severe sepsis	Lower mortality when a macrolide was added
Bratzler et al. [32][a]	2008	Multicentric, retrospective, enrolling 27,330 patients	Compare mortality after 3rd generation cephalosporin versus quinolone or a BL–macrolide regimen	Higher mortality after BL alone with respect to the administration of a quinolone alone or a BL–macrolide combination
Bhavnani et al. [33]	2008	Multicentric, prospective study	Explore cost-effectiveness of oral gemifloxacin compared with ceftriaxone with/without macrolide	Comparable mortality with different regimens; lower costs with quinolone therapy
Lloyd et al.[a] [34]	2008	Multicentric, retrospective, enrolling 738 patients	Explore costs after moxifloxacin versus ceftriaxone plus levofloxacin	Lower costs after moxifloxacin administration; comparable treatment success rate
Lodise et al.[a] [35]	2007	Multicentric, retrospective study enrolling 515 patients	Compare outcomes after BL–macrolide versus quinolone administration	Lower mortality after combination therapy in PSI V; no difference in mortality in PSI lower than V
Metersky et al.[a] [36]	2007	Multicentric, retrospective, enrolling 2209 patients with bacteraemic CAP	Explore if atypical coverage was associated with different outcomes	Lower mortality after atypical coverage; further decrease in mortality if coverage was with a macrolide-based regimen
Dwyer et al.[a] [37]	2006	Prospective, multicentric study enrolling 340 patients with bacteraemic pneumococcal CAP	Compare outcomes after BL monotherapy compared with BL–macrolide regimen	No differences in mortality after BL alone versus BL plus macrolide
Welte et al. [38]	2005	Multicentric, randomized non-blinded clinical trial enrolling 317 patients	Compare outcomes after moxifloxacin versus ceftriaxone with/without erythromycin administration	Same mortality with a faster clinical improvement after moxifloxacin administration
Querol-Ribelles et al. [39]	2005	Prospective, unicentric, enrolling 459 patients	Compare outcomes after levofloxacin monotherapy versus ceftriaxone plus clarithromycin	Lower mortality after levofloxacin administration; no difference in terms of length stay
Garcia Vazquez et al. [40]	2005	Prospective, multicentric study enrolling 1391 patients	Assessing changes in outcomes after administration of a BL–macrolide regimen versus a BL alone	Lower mortality after combined therapy in all severity pneumonias

BL beta-lactam, *PSI* pneumonia severity index, *CAP* community-acquired pneumonia

[a] The study includes ward and ICU patients

patients who received combination therapy with a macrolide, when compared with that in those who received monotherapy or combination therapy without a macrolide.

Leroy et al. [42] performed a clinical trial enrolling 398 critical patients without shock or a requirement for mechanical ventilation and compared levofloxacin with ceftriaxone plus ofloxacin; no differences in mortality, clinical resolution and adverse event rate were observed.

Five observational studies obtained similar results. Our group of research in pneumonia, in a case-control analysis published in 2014 [3], observed an increased survival after combination therapy; this association was found in the main

Table 5 Published studies in ICU patients that assess monotherapy versus combined therapy

Author	Year	Study design	Study population	Objective	Outcomes
Sligl et al. [41]	2014	Meta-analysis	Twenty eight observational studies, without clinical trials, enrolling 9850 patients	Compare outcomes after macrolide-containing regimen versus non-macrolide regimens	Combined therapy with a macrolide regimen was associated with lower mortality
Leroy et al. [42]	2005	Clinical trial	Multicentric, randomized, open-label clinical trial, enrolling 398 patients without shock or mechanical ventilation	Explore outcomes after levofloxacin monotherapy versus cefotaxime plus ofloxacin	Comparable mortality, clinical resolution and adverse effects rate after administration of either monotherapy or combined therapy
Gattarello et al. [3•]	2014	Observational	Multicentre, case-control analysis of a prospective data compared with an historic cohort, enrolling 80 patients	Compare mortality after monotherapy versus combined therapy	Combined therapy was associated with improved survival in patients with shock, under mechanical ventilation, and without shock neither mechanical ventilation
Adrie et al. [43]	2013	Observational	Multicentre, retrospective study enrolling 956 patients	Compare mortality and resistance development after combined versus monotherapy	Combined therapy improved survival in patients with shock; combined therapy increased probability of adequate treatment; no resistance development was observed in combination therapy
Rello et al. [44]	2012	Observational	Multicentric, retrospective enrolling 1989 patients over 65 years	Compare mortality after BL–macrolide versus BL–quinolone	No differences in mortality; higher length of stay after BL–quinolone administration
Rello et al. [45]	2012	Observational	Multicentre, retrospective, enrolling 25 patients with severe sporadic *Legionella* pneumonia	Compare mortality in *Legionella* pneumonia	Lower mortality after combination therapy in patients with shock
Martin-Loeches et al. [46]	2010	Observational	Multicentre, prospective study enrolling 218 patients	Explore changes in mortality after macrolide addition in intubated patients with CAP	Lower mortality in patients that received macrolide-based combination therapy
Rodriguez et al. [47]	2007	Observational	Multicentre, prospective study enrolling 529 patients	Compare mortality after combination therapy or monotherapy administration	Lower mortality in patients with shock after combination therapy administration
Harbarth et al. [48]	2005	Observational	Multicentre, retrospective analysis of 1840 patients with pneumococcal CAP and severe sepsis/septic shock	Compare mortality after monotherapy versus combined therapy	No differences in mortality after monotherapy or combination therapy
Mortensen et al. [49]	2005	Observational	Multicentric, retrospective study enrolling 172 patients with severe CAP	Compare mortality after BL–quinolone versus other guidelines-concordant antibiotic regimens	Higher mortality when BL plus quinolone versus other guidelines-concordant regimens

BL beta-lactam, *CAP* community-acquired pneumonia, *RCT* randomized controlled trial

cohort and in all analysed subgroups: patients with shock or a need for mechanical ventilation, and critically ill patients without shock or a need for mechanical ventilation. Adrie et al. [43] documented a decreased mortality after combination therapy; interestingly, this association was stronger in patients with shock or with pneumococcal infection. Rello et al. documented the same trend [45] in patients with severe CAP by *L. pneumophila* and shock, Rodriguez et al. [47] in patients with severe CAP with shock and Martin-Loeches et al. [46] in intubated patients with CAP.

Only one study published by Harbarht in 2005 [48] documented a comparable mortality between monotherapy and combination therapy in patients with CAP and severe sepsis or shock.

Finally, two studies explored outcomes after administration of a beta-lactam–macrolide regimen compared with a beta-lactam–fluoroquinolone regimen; Mortensen et al. [49] found a lower mortality after administration of the macrolide-based regimen in a cohort of 172 critical patients with severe CAP. Conversely, Wilson et al. [44] did not find differences in

mortality in elderly patients with CAP. It was noteworthy that a higher length of stay was documented in the beta-lactam–fluoroquinolone group.

Discussion

In the present article, we reviewed the available literature regarding monotherapy versus combined therapy in CAP. Although recent publications have not resolved all the remaining controversies, a majority of the meta-analyses and the observational studies support combination therapy with macrolide therapy, but the outcomes measured in clinical trials did not favour either arm.

In summary, outpatients with CAP without risk factors for a poor clinical outcome did not benefit from combined therapy; hence, monotherapy with either a macrolide, a fluoroquinolone or a beta-lactam may be proposed as no differences in mortality were observed by any specific antibiotic class. This controversy reflects the differences between the European and American guidelines. In fact, unlike the American guidelines, the European guidelines do not recommend empiric atypical coverage as a first-line treatment.

On one side, fluoroquinolone administration appears to be associated with a higher eradication rate, a lower treatment failure and possibly less cost of treatment; however, concerns about an increased resistance rate after fluoroquinolone administration have been raised [50]. In the case of a social environment with high rates of pulmonary tuberculosis, the empiric use of a fluoroquinolone could actually mask pulmonary tuberculosis delaying its diagnosis [51]. Thus, antibiotic prescription should be done considering local epidemiological data, i.e. the most frequent aetiologies of CAP and the local resistance pattern.

In the case of outpatients with CAP and with risk factors for poor clinical evolution, there is evidence supporting atypical coverage, although no differences in mortality were observed, and there was a decreased cost of treatment because of reduced treatment failures and secondary hospital admissions. Although the American guidelines recommend a fluoroquinolone or a beta-lactam plus a macrolide equally, some authors advocate the use of a beta-lactam plus macrolide combination. A decision should be guided by local guidelines based on epidemiological data.

In case of a hospitalised non-ICU patient, contrasting conclusions do not allow supporting the administration of monotherapy rather than combination therapy. As a general indication, in case of a mild to moderate pneumonia without risk factors for a poor clinical evolution, the use of a beta-lactam or a fluoroquinolone in monotherapy is probably the best choice. Conversely, in case of moderate to severe CAP with PSI score of IV or V, bacteraemia due to *Streptococcus pneumoniae*, the presence of risk factors for a poor outcome, or a high suspicion of atypical pneumonia, the use of beta-lactam monotherapy is probably not enough. Again, because of the current lack of evidence, the use of a fluoroquinolone monotherapy rather than a beta-lactam and macrolide association should be based on local epidemiological considerations. It is noteworthy that levofloxacin 750 mg per day is more effective than standard dose (500 mg), without an increase of adverse effects [22].

Finally, in case of severe CAP and ICU admission, stronger evidence for promoting the use of combined therapy was published. In fact, a meta-analysis and several observational studies documented an increased survival after dual antibiotic administration. This statement seems to be conclusive in patients with septic shock, although it was not always confirmed in the rest of ICU patients. However, despite the contrasting results in ICU patients without shock and because of the high mortality of severe CAP, it seems safer to administer combination therapy to all ICU patients with CAP. Furthermore, according with the meta-analysis of Sligl et al., the combination regimen associated with the highest survival appears to be a beta-lactam plus a macrolide as opposed to without a macrolide.

The main argument to justify combination therapy in mild to moderate pneumonia is the coverage of atypical agents; although contrasting results were obtained regarding mortality, it appears that in certain subgroups (i.e. the presence of risk factors for a poor outcome or bacteraemic pneumococcal pneumonia), atypical coverage is likely beneficial in terms of cost of treatment, eradication rate and clinical resolution. Alternatively, in case of severe CAP, the use of combined therapy is almost always associated with a decreased mortality; in fact, it was observed that the lack of atypical coverage in atypical pneumonia was associated with an increased mortality [52]; moreover, the association between macrolide use and a reduced mortality may be explainable by the antiinflammatory effects attributed to macrolides [41, 46]. In fact, severe CAP is often associated with sepsis or septic shock, and macrolide administration may decrease the inflammatory reaction. A reason that might explain why not all studies observed a reduced mortality after macrolide administration is because only patients with a high inflammatory response may benefit from it. However, this is a hypothesis and should be confirmed with a well-designed randomised controlled trial.

The use of combined therapy aroused concerns about the development of antibiotic resistance. In the present review, only one study [43] explored this issue, without differences in the development of new bacterial resistances after either monotherapy or combination therapy. Follow-up studies exploring microbial resistance after monotherapy or combination therapy would be beneficial.

Conclusions

Although many controversies remain in the optimal treatment of CAP, the use of combined therapy seems to be associated with an improved mortality in cases of severe CAP that requires ICU admission, especially when a beta-lactam–macrolide is prescribed. Moreover, it appears that combination therapy may be associated with better outcomes in cases of outpatient or ward hospitalised patients with risk factors for a poor outcome, with bacteraemic pneumococcal pneumonia and with a high suspicion of infection by atypical agents. In this setting, it appears that the best choice of treatment may be a beta-lactam–macrolide regimen.

In the next years, forthcoming challenges will be to better identify the subgroups of patients that are benefited by combination therapy, and to study the impact of monotherapy and combination therapy in the emergence of new antimicrobial resistances.

Compliance with Ethics Guidelines

Conflict of Interest Simone Gattarello has no relevant disclosures to report.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by the author.

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