Universidad de Navarra

Facultad de Farmacia y Nutrición

IMPACTO CLÍNICO Y ECONÓMICO DE LAS INTERVENCIONES DEL FARMACÉUTICO CLÍNICO SOBRE ANTIMICROBIANOS EN EL PACIENTE CRÍTICO

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TESIS DOCTORAL

IMPACTO CLÍNICO Y ECONÓMICO DE LAS INTERVENCIONES DEL FARMACÉUTICO CLÍNICO SOBRE ANTIMICROBIANOS EN EL PACIENTE CRÍTICO

Trabajo presentado por Dña. LEIRE LEACHE ALEGRÍA para obtener el grado de Doctor

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Certifican:

Que el presente trabajo, titulado "IMPACTO CLÍNICO Y ECONÓMICO DE LAS INTERVENCIONES DEL FARMACÉUTICO CLÍNICO SOBRE ANTIMICROBIANOS EN EL PACIENTE CRÍTICO", presentado por Dña. LEIRE LEACHE ALEGRÍA para optar al Grado de Doctor en Farmacia, ha sido realizado bajo su dirección en el Departamento de Farmacia y Tecnología Farmacéutica de la Universidad de Navarra. Considerando finalizado el trabajo, autorizan su presentación a fin de que pueda ser juzgado y calificado por el Tribunal correspondiente.

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Dra. Ana Ortega Eslava (Directora)

Dra. Irene Aquerreta González (Co-directora)

Pamplona, 2017

A mis padres y hermanos, por su amor, comprensión y apoyo incondicional

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ÍNDICE

0. GLOSARIO

ADE	Adverse Drug Event
AmpC	Ampicillin class C
ATS	American Thoracic Society
BCS	Base-case scenario
BMI	Body Mass Index
CCA	Critical Care Area
CBA	Controlled Before-After study
CI95%	95% Confidence Interval
CO	Clinical Outcome
CP	Clinical Pharmacist
CPI	Clinical Pharmacist Intervention
CrCl	Creatinine Clearance
CT	Controlled Trial
CTRL	Control group simultaneous in time with intervention group
CTRL-PRE	Control group simultaneous in time with pre-intervention group
DDD	Dosis Diaria Definida
DRP	Drug Related Problem
ECDC	European Centre for Disease Prevention and Control
ESBL	Extended-Spectrum Beta-Lactamase
FDA	Food and Drug Administration
ICU	Intensive Care Unit
IDSA	Infectious Diseases Society of America
INT	During intervention
INTB	Intubation
IQ range	Interquartile range
iv	Intravenous

MAX	Maximum
MIN	Minimum
MLSb	Macrolide, lincosamide and streptogramin B
MO	Microbiological Outcome
MV	Mechanical Ventilation
NA	Not Applicable
NICE	National Institute for Health and Care Excellence
no.	Number
NR	Not Reported
NS	Not Significant
Obs.	Observations
OCSD	Observational Controlled study based on Surveys and Databases
OMS	Organización Mundial de la Salud
OR	Odds ratio
p	Probability
PI	Pharmacists Intervention
PICO	Participants, Interventions, Comparisons, and Outcomes
po	Oral
POST	After the intervention
PRE	Before the intervention
PRM	Problemas Relacionados con Medicamentos
PROA	Programa de Optimización del uso de Antiinfecciosos/ Program for Optimizing the use of Antibiotics
PSR	Patient Specific Recommendation
RCT	Randomized Controlled Trial
SA	Sensitivity analysis

SAPS3	*Simplified Acute Physiology* Score 3
SD	Standard Deviation
SEMICYUC	Sociedad Española de Medicina Intensiva, Crítica y Unidades Coronarias
SOFA	*Sequential Organ Failure Assessment*
spp.	Species
SYREC	Seguridad y Riesgo en el Enfermo Crítico
TDM	Therapeutic Drug Monitoring
TRO	Treatment Related Outcome
UBA	Uncontrolled Before-After study
UCI	Unidad de Cuidados Intensivos
USA	United States of America
USD	United States Dollars
Van	Vancomycin
VAP	Ventilator-Associated Pneumonia
VAT	Ventilator-Associated Tracheobronchitis
VIH	Virus de la Inmunodeficiencia Humana
vs.	Versus
WHO	World Health Organization
€	Euro
%	Percentage

1. INTRODUCCIÓN

1.1. Unidades de Cuidados Intensivos, el paciente crítico y el farmacéutico clínico

1.1.1. Unidades de Cuidados Intensivos

La Unidad de Cuidados Intensivos (UCI) se define como una organización de profesionales sanitarios que ofrece asistencia multidisciplinar en un espacio específico del hospital, que cumple unos requisitos funcionales, estructurales y organizativos, de forma que garantiza las condiciones de seguridad, calidad y eficiencia adecuadas para atender a pacientes que requieren cuidados y monitorización intensiva.[1]

Los requisitos de las UCIs fueron establecidos en el documento "Unidad de cuidados intensivos. Estándares y recomendaciones" elaborado por el Ministerio de Sanidad y Política Social del Gobierno de España en el año 2010. Entre otros requisitos, el hospital responsable de una UCI debe tener disponible, las veinticuatro horas del día, servicios asistenciales y de soporte clínico y no clínico para asegurar la calidad y continuidad de la atención al paciente, cuyo nivel de exigencia varía en relación con la complejidad de la propia UCI.[1]

Las UCIs proporcionan atención a pacientes que se sitúan en los niveles 2 y 3 de asistencia hospitalaria de acuerdo con la clasificación del Departamento de Salud del Reino Unido. El nivel 2 hace referencia a pacientes que requieren observación más frecuente o intervención, incluyendo el soporte a un sistema orgánico o cuidados postoperatorios, o aquellos que provienen de niveles de cuidados más elevados. El nivel 3 comprende aquellos pacientes que requieren soporte respiratorio avanzado o soporte respiratorio básico junto con, al menos, soporte a dos sistemas orgánicos. Este último nivel incluye a todos los pacientes complejos que requieren soporte por fallo multiorgánico.[1]

Seguridad en las Unidades de Cuidados Intensivos

Los pacientes atendidos en las UCIs son particularmente vulnerables a las lesiones iatrogénicas debido a la gravedad e inestabilidad de su situación y al requerimiento frecuente de intervenciones y administración de medicamentos de alto riesgo.[2]

Además de la gravedad del enfermo crítico, las barreras de comunicación entre los diferentes profesionales, la realización de un número elevado de actividades por

paciente y día, la práctica de procedimientos diagnósticos y tratamientos invasivos, y la cantidad y complejidad de la información recibida, entre otros, convierten a las UCIs en un área de riesgo para la aparición de eventos adversos.[3]

La seguridad del paciente o seguridad clínica se define como la "prevención y mejora de los resultados adversos o lesiones derivados de procesos de atención sanitaria". Esos eventos comprenden «errores», «desvíos» y «accidentes».[4]

El informe de la Organización Mundial de la Salud (OMS) en relación a la calidad de la atención y seguridad del paciente establece que "las intervenciones de atención de salud se realizan con el propósito de beneficiar al paciente, pero también pueden causarles daño. La combinación compleja de procesos, tecnologías e interacciones humanas que constituyen el sistema moderno de prestación de atención de salud puede aportar beneficios importantes. Sin embargo, también conlleva un riesgo inevitable de que ocurran efectos adversos".[3]

Según datos de la Comisión Europea, se estima que entre el 8 y el 12% de los pacientes hospitalizados sufre acontecimientos adversos; tales como infecciones relacionadas con la asistencia, errores de medicación, errores relacionados con la cirugía, fallo de dispositivos médicos, errores en el diagnóstico, *etc*. Según datos de dicha comisión, una gran proporción de eventos adversos, tanto en atención primaria como en especializada, se consideran prevenibles.[5]

Por otro lado, el informe sobre "Coste de la asistencia sanitaria insegura y coste-efectividad de los programas de seguridad del paciente" de la Comisión Europea del año 2016 indica que el coste de los eventos adversos oscila entre aproximadamente un 0,2% y un 6,0% del gasto sanitario total.[5] Este dato coincide con el resultado obtenido en el estudio de Allué *et al*.[6], según el cual los eventos adversos en los hospitales españoles entre los años 2008 y 2010 supusieron un coste adicional de un 6,7% del total del gasto sanitario (88.268.906 €). Estos datos dan idea de la magnitud del problema.

En cuanto a las UCIs, en el año 2007 la Agencia de Calidad del Sistema Nacional de Salud y la Sociedad Española de Medicina Intensiva, Crítica y Unidades Coronarias

(SEMICYUC) llevaron a cabo un estudio multicéntrico de cohortes prospectivo en UCIs españolas, con el fin de estimar la incidencia de eventos adversos e incidentes, los factores que facilitan su aparición, así como su evitabilidad y consecuencias, mediante un periodo de seguimiento de 24 horas. Participaron 79 servicios, incluyendo 1.017 pacientes. Un 58% de los pacientes presentó al menos un incidente, de los cuáles un 43% presentó al menos un error de medicación. El número total de incidentes notificados fue de 1.424, de los cuales los errores de medicación fueron los más prevalentes (24,6%). Estos últimos ocurrieron de manera más frecuente durante la prescripción (34%), seguido de los que ocurrieron durante la administración (28%), la transcripción (17%) y la dispensación (15%). Se estimó que el riesgo que presentaba un paciente de sufrir un error de medicación por ingresar en una UCI era de un 22%. Se obtuvo una tasa de 1,13 errores de medicación por 100 pacientes/día de estancia en UCI. Un 16% de los errores de medicación produjeron daño al paciente y un 82% se consideraron "sin duda evitables". En cuanto a la evitabilidad de los incidentes y eventos adversos en general, un 90% de los incidentes y un 60% de los eventos adversos fueron clasificados como evitables o posiblemente evitables.[3,7] En otros estudios acerca de seguridad llevados a cabo en UCIs, se estimó que entre un 45% y un 90% de los eventos adversos e incidentes fueron evitables.[2,3,8]

De manera frecuente, los eventos adversos conllevan consecuencias muy relevantes. En la revisión llevada a cabo por Vlayen *et al.*,[9] se obtuvo que el porcentaje de eventos adversos quirúrgicos y médicos que requirieron ingreso en UCI se encontraba entre un 1,1% y un 37,2%. Por otro lado, Graf *et al.*,[10] en su estudio observaron que la probabilidad de que ocurriese un evento adverso se incrementaba por cada día de estancia en UCI en un 8%.

La elevada relevancia y evitabilidad de esta clase de incidentes y eventos adversos demuestra la existencia de oportunidades de mejora en este ámbito. Diferentes estrategias han demostrado ser efectivas para prevenir los incidentes y errores relacionados con medicamentos, como los procedimientos estandarizados para la utilización de los mismos, la utilización de los sistemas de notificación de incidentes, así como la inclusión del farmacéutico clínico en el equipo multidisciplinar que atiende al paciente, entre otros.[3]

1.1.2. El paciente crítico

Los pacientes críticos difieren de forma considerable del resto de enfermos que se encuentran en entornos de hospitalización convencional, presentando unas tasas de mortalidad significativamente superiores. Un elevado porcentaje de estos pacientes presenta estados de sepsis, shock y/o fallo renal agudo, asociados a cambios fisiopatológicos relevantes que requieren intervenciones médicas agresivas. Estos cambios que acontecen en el paciente crítico afectan de manera muy relevante a la absorción, distribución, metabolismo y eliminación de los fármacos, modificando los índices farmacocinéticos y farmacodinámicos de los mismos.[11,12]

La biodisponibilidad de aquellos fármacos administrados por vías de administración diferentes a la intravenosa se encuentra influenciada por factores tales como el pH, el flujo sanguíneo, la superficie de absorción y la motilidad gastrointestinal. Debido a que estos aspectos se encuentran alterados de manera significativa en el paciente crítico, la absorción de los fármacos en esta población puede verse afectada.[13]

A nivel cardiovascular, de manera frecuente, los pacientes críticos presentan respuestas inflamatorias sistémicas de causa infecciosa o no infecciosa. Debido a esta situación y como consecuencia del daño que se produce en el endotelio y de la fuga capilar, ocurre la extravasación de fluidos al espacio intersticial. Dicha extravasación de fluidos conlleva hipotensión, y habitualmente requiere la repleción con elevados volúmenes de líquidos, contribuyendo a un mayor aumento del volumen intersticial. Del mismo modo, en este grupo de pacientes también resulta frecuente la presencia de hipoalbuminemia. Según Blot *et al.*,[12] más de un 40% de los pacientes críticos presenta concentraciones séricas de albúmina ≤2,5 g/dL. La hipoalbuminemia propicia un incremento de la fracción de fármaco libre y resulta clínicamente relevante en aquellos fármacos con un porcentaje de unión a proteínas plasmáticas elevado (>85-90%) y cuyo aclaramiento es fundamentalmente mediante filtración glomerular. Tanto la administración de fluidos intravenosos como la hipoalbuminemia conllevan un aumento en el volumen aparente de distribución de los fármacos, afectando sobre todo a fármacos hidrofílicos, como es el caso de antimicrobianos de tipo betalactámicos, aminoglucósidos, glicopéptidos y colistina. Esto hace que los pacientes críticos en

ocasiones requieran dosis de carga y dosis de mantenimiento de dichos fármacos superiores para alcanzar el objetivo terapéutico.[11,12]

El volumen aparente de distribución de los fármacos hidrofílicos puede también verse incrementado por diversas intervenciones que con frecuencia se llevan a cabo en los pacientes críticos, como son la ventilación mecánica, los circuitos extracorpóreos y/o el drenaje postquirúrgico.[12]

El paciente crítico también puede tener la función hepática alterada debido a infecciones asociadas a colestasis o daño hepatocelular, hepatitis isquémica, hemólisis o daño directo por fármacos hepatotóxicos. Dichas situaciones conllevan alteraciones en la concentración de proteínas plasmáticas, en la actividad de enzimas hepáticas y en el flujo sanguíneo hepático, comprometiendo el metabolismo de los fármacos.[12]

Por otro lado, la repleción con elevados volúmenes de líquidos y el uso habitual de agentes vasoactivos puede conducir a un incremento en el aclaramiento renal de los fármacos eliminados por esta vía. Esto ocurre de manera más frecuente en pacientes jóvenes que presentan traumatismos, sepsis, quemaduras, enfermedades hematológicas malignas, pancreatitis, cirugías mayores, *etc*. De manera opuesta, la reducción del flujo sanguíneo a los riñones, debido por ejemplo a una hipotensión mantenida, conlleva fallo renal agudo, con la consecuente disminución del aclaramiento renal de los fármacos eliminados por esta vía. Ambas situaciones tienen repercusión en la farmacocinética de aquellos fármacos hidrofílicos con eliminación renal.[11,12,14]

Los cambios que se dan en el paciente crítico en cuanto a la absorción, distribución, metabolismo y eliminación de los fármacos, pueden por tanto afectar a las concentraciones que se alcanzan en el lugar de acción.[14,15] Ello justifica de manera muy relevante la necesidad de optimización de las terapias antimicrobianas, entre otras, en este tipo de pacientes.

Del mismo modo, los pacientes críticos habitualmente requieren un elevado número de fármacos, muchos de ellos de alto riesgo (anticoagulantes, sedantes, fármacos con

efecto cardiovascular, *etc.*), lo que incrementa marcadamente la probabilidad de interacción fármaco-fármaco.[12]

Por todo ello, en este escenario resulta especialmente relevante la presencia del farmacéutico como experto en el medicamento, de cuyas actuaciones se derivan beneficios significativos en cuanto a resultados en salud, tal y como se ha plasmado en distintos trabajos.[16,17]

1.1.3. El farmacéutico clínico en las Unidades de Cuidados Intensivos

Conforme a las guías de buena práctica clínica en farmacia elaboradas por la Federación Internacional Farmacéutica y la OMS,[18] la colaboración multidisciplinar entre profesionales de la salud constituye el factor clave para mejorar de manera exitosa la seguridad del paciente.

En Estados Unidos, en torno al año 1980, los profesionales farmacéuticos se incorporaron a distintas UCIs, tanto de pacientes adultos como de pediátricos, y también a quirófanos y servicios de urgencia. Desde el inicio los farmacéuticos de las UCIs desarrollaron programas de formación especializada e incrementaron su participación e intervención en dichas áreas. A partir de entonces, el crecimiento de la farmacia clínica como especialidad ha ocurrido de manera paralela a este desarrollo.[19,20]

En el año 2000, un grupo de trabajo centrado en el papel de los Servicios de Farmacia en cuidados intensivos formado por miembros de la *Society of Critical Care Medicine* y el *American College of Clinical Pharmacy* definió el nivel de práctica clínica y habilidades especializadas que deben caracterizar al farmacéutico de cuidados intensivos como clínico, educador, investigador y gestor, y estableció los requerimientos fundamentales, deseables y óptimos tanto de los Servicios de Farmacia como del personal para la provisión de atención farmacéutica a pacientes críticos.[19,20] Entre las actividades fundamentales del farmacéutico en las UCIs destacan la

evaluación prospectiva del tratamiento farmacológico, intervención en lo referente a la indicación y dosis de medicamentos, detección de interacciones, seguimiento de la efectividad de los tratamientos, monitorización farmacocinética de fármacos, prevención, identificación y manejo de los eventos adversos, desarrollo de estrategias de mejora para reducir errores de medicamentos y eventos adversos prevenibles, educación en lo referente a medicamentos dirigida a otros profesionales, registro de sus actividades clínicas, así como el desarrollo de políticas y procedimientos en relación al uso seguro y efectivo de los medicamentos en las UCIs, entre otros.[19,20] Del mismo modo, el *National Institute for Health and Care Excellence* (NICE) estableció la optimización de los tratamientos farmacológicos como un componente esencial del cuidado del paciente, que comprende diversas facetas de la práctica farmacéutica, como la conciliación de la medicación, la revisión de los tratamientos, la monitorización de su seguridad y el desarrollo de sistemas de apoyo para la toma de decisiones clínicas.[21]

En cuanto a la integración del farmacéutico clínico en el equipo multidisciplinar que atiende al paciente crítico, en el año 2001 Brilli *et al*.[22] destacaron la "colaboración por parte de enfermería, área respiratoria y farmacia con el personal médico en un enfoque de equipo" como parte del modelo de práctica de las UCIs.

En el documento desarrollado en el año 2010 en España acerca de los estándares de trabajo en las UCIs, dentro del apartado de "Aspectos organizativos y de gestión que afectan al proceso de atención al paciente en la UCI" se incluye la implementación de pases de visita multidisciplinares como medida para aumentar la seguridad del paciente grave, en el cuál se incluye el farmacéutico. Del mismo modo, la implantación del pase de visita multidisciplinar se ha visto vinculada con una mayor satisfacción en relación a la atención percibida por parte de los pacientes y con una mejor comunicación y colaboración entre los diferentes profesionales.[1]

En un estudio llevado a cabo en 2015 que incluía 279 UCIs de Reino Unido, se observó que un 96,6% de las mismas tenía al menos un farmacéutico en su dotación de personal asistencial. Además, en dicho estudio se observó que los farmacéuticos dedicaban un 24,5% de su jornada a los pases de vista multidisciplinares, un 58,5% de

la jornada a la revisión independiente de los pacientes y tratamientos, y el 17% restante a otras actividades vinculadas al ámbito de cuidados intensivos.[23]

En los estudios disponibles hasta la fecha se pone de manifiesto que la intervención del farmacéutico en las UCIs resulta relevante, debido a que ha demostrado tener un impacto positivo tanto a nivel clínico como económico. Los resultados obtenidos en este ámbito demuestran que las intervenciones farmacéuticas en relación a la optimización de los tratamientos están vinculadas a una mejoría significativa del cuidado del paciente, y a una reducción de la duración de estancia en UCI, de la incidencia de eventos adversos y de la mortalidad; del mismo modo, conllevan un ahorro económico.[16,17,24-30]

El farmacéutico clínico en el Área de Cuidados Críticos de la Clínica Universidad de Navarra

Hasta los años 90, en España tradicionalmente el farmacéutico desarrollaba su papel asistencial de forma centralizada en el Servicio de Farmacia, sin trasladar su actividad de forma continua al contacto directo con el paciente ingresado. En el año 2000 se aprobó la prolongación de la especialización en Farmacia Hospitalaria a cuatro años con el objetivo, entre otros, de promover la formación clínica del farmacéutico, dirigida a potenciar su trabajo en la proximidad del paciente y a facilitar su integración con el resto del equipo asistencial. Este hecho supuso una oportunidad para la incorporación del farmacéutico clínico al equipo asistencial del Área de Cuidados Críticos, así como al equipo de Oncología de la Clínica Universidad de Navarra. El principal objetivo, inicialmente fue realizar un seguimiento continuado de la farmacoterapia del paciente de manera presencial e integrada en el equipo asistencial. Desde un primer momento se procedió al registro de las intervenciones realizadas por el farmacéutico clínico, con el fin de cuantificar el impacto clínico y económico de las mismas.[31]

El Área de Cuidados Críticos de la Clínica Universidad de Navarra comprende la Unidad de Cuidados Intensivos y el Área de Hospitalización Especializada. La actividad diaria del farmacéutico clínico en el Área de Cuidados Críticos consiste en asistir a primera hora de la mañana a la reunión de cambio de guardia, en la que el médico saliente de guardia traslada al resto del equipo la evolución de los pacientes en las últimas 24

horas. Posteriormente, el farmacéutico permanece un mínimo de 5 horas al día en la unidad, revisando las historias clínicas y la evolución de los pacientes, las pruebas de laboratorio y cultivos, y el tratamiento farmacoterapéutico, contrastando la hoja de prescripción (orden médica) con la hoja de administración de enfermería, supervisando la administración de medicamentos y contactando directamente con el paciente o familiares cuando es posible y necesario. Al final de la mañana, el farmacéutico participa en el pase colegiado de visita junto con el personal médico y de enfermería de la unidad.[31]

A lo largo de la mañana así como durante el pase de visita el farmacéutico comunica al médico o a la enfermera responsable las recomendaciones que considera pertinentes para la optimización de los tratamientos, que incluyen además de los ajustes posológicos y la vía de administración, los Problemas Relacionados con Medicamentos (PRM) detectados durante el proceso de revisión de las prescripciones y las posibles alternativas de tratamiento. En el caso de que dichas recomendaciones sean aceptadas, la prescripción médica es modificada por el médico y validada por el farmacéutico. Al final de la jornada, el farmacéutico procede al registro de las intervenciones realizadas durante la jornada, a la resolución de cuestiones en relación a la utilización de medicamentos planteadas en la unidad y a la revisión bibliográfica de temas de interés farmacoterapéutico en pacientes críticos.[31]

En un estudio llevado a cabo en la Clínica Universidad de Navarra para analizar de forma conjunta el impacto clínico y económico de la integración del farmacéutico en el equipo asistencial del Área de Cuidados Críticos y de Oncología, se observó que entre febrero de 2002 y octubre de 2005 el farmacéutico llevó a cabo 8.678 intervenciones en 2.294 pacientes (71% en el Área de Cuidados Críticos y el resto en Oncología). Se detectaron un total de 8.249 PRM, que estaban relacionados con la indicación de los medicamentos (51%), la seguridad (30%), la efectividad de los tratamientos (19%) o la adherencia del paciente a dichos tratamientos (0,4%). Se registraron 2.750 errores de medicación, de los cuales un 63% se evitaron antes de que alcanzaran al paciente. El 95% de las intervenciones llevadas a cabo por el farmacéutico fueron aceptadas por el médico. Un 92% de las intervenciones supusieron mejoría en el cuidado del paciente. Durante dicho periodo de tiempo, el coste evitado con las intervenciones

farmacéuticas se estimó en 232.147 €, con un beneficio neto de 1.020 €/farmacéutico/mes.[31] Hasta el momento no disponemos de datos publicados acerca del impacto clínico y económico de las intervenciones del farmacéutico clínico integrado en el Área de Cuidados Críticos de forma independiente.

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1.2. Infecciones en el paciente crítico y papel del farmacéutico clínico en la optimización del tratamiento antimicrobiano

1.2.1. Infecciones y terapia antiinfecciosa en el paciente crítico

En la actualidad, las infecciones siguen siendo un problema relevante en los pacientes críticos.[15] Las infecciones en las UCIs incluyen, entre otras, tanto aquellas que por su severidad requieren cuidados intensivos como aquellas adquiridas en la propia UCI. Un estudio llevado a cabo en 1417 UCIs europeas obtuvo que el 44,8% de los pacientes críticos presentaban al menos una infección, de los cuales aproximadamente la mitad (46%) adquirieron la infección en la UCI.[32] El riesgo de infecciones adquiridas en la UCI incrementa con la duración de la estancia en la misma y el requerimiento de procedimientos invasivos (*p.ej.*: neumonía asociada a ventilación mecánica, infección del tracto urinario asociada a sonda vesical, bacteriemia asociada a catéter vascular, ventriculitis asociada a drenajes ventriculares externos, *etc.*).[32,33] El estudio de prevalencia de las infecciones nosocomiales en España del año 2016 indica que la prevalencia de infecciones nosocomiales en los hospitales españoles es de un 8,74%, siendo la UCI el área de asistencia del hospital con mayor tasa de dichas infecciones.[34]

Las infecciones en pacientes críticos conllevan un aumento de la morbilidad de los mismos, mayor duración de la ventilación mecánica, y estancias tanto hospitalarias como UCI más prolongadas, junto con una mayor tasa de mortalidad en comparación con los pacientes ingresados en unidades de hospitalización convencional.[35] En concreto, la sepsis afecta a aproximadamente un tercio de los pacientes de UCI y se encuentra asociada a una elevada tasa de mortalidad.[15] La tasa de mortalidad asociada a dicha situación es de aproximadamente un 20-30%, mientras que en los casos más severos puede llegar hasta un 30-50%. Dicha tasa viene influenciada tanto por la gravedad de la enfermedad aguda como por las comorbilidades subyacentes de los pacientes.[12]

En lo referente al empleo de antiinfecciosos, se ha visto que aproximadamente dos tercios de los pacientes admitidos en las UCIs reciben tratamiento antimicrobiano.[15] Dada la gravedad de su situación clínica, la práctica habitual consiste en establecer un tratamiento empírico inicial, habitualmente basado en antimicrobianos de amplio espectro.[32] Además, resulta frecuente la combinación de diferentes antimicrobianos

debido, en parte, al problema actual de resistencia antimicrobiana. Actualmente, la combinación de antimicrobianos está indicada, entre otros, en pacientes neutropénicos con sepsis, pacientes con infecciones debidas a patógenos multirresistentes y pacientes con infecciones respiratorias severas y shock séptico.[36]

La efectividad del tratamiento antimicrobiano es un determinante crucial en pacientes críticos con infecciones severas.[37] El éxito del tratamiento antimicrobiano en estos pacientes depende, entre otras cosas, tanto del reconocimiento temprano de la infección como de la instauración temprana de la terapia.[38] La administración temprana de un tratamiento antimicrobiano efectivo se ha visto asociada a un aumento sustancial de la supervivencia.[37] Del mismo modo, el retraso en la identificación de una situación de sepsis y shock séptico, y en la instauración del tratamiento antiinfeccioso, se ha relacionado con un mayor riesgo de mortalidad.[39] En el estudio llevado a cabo por Kumar *et al.*,[40] la administración de un tratamiento antimicrobiano efectivo dentro de la primera hora tras la detección de hipotensión en pacientes adultos con shock séptico estuvo asociada a un incremento de la supervivencia. En este estudio en concreto, sólo el 50% de los pacientes con shock séptico recibió tratamiento antimicrobiano efectivo dentro de las 6 primeras horas tras la detección de hipotensión.

Por otro lado, en el paciente crítico sobre todo, resulta prioritario la optimización de las pautas posológicas de los antiinfecciosos. Como ya se ha comentado anteriormente, los cambios fisiopatológicos que acontecen en el paciente crítico conllevan modificaciones significativas en la farmacocinética de gran cantidad de antimicrobianos. Estas variaciones pueden conllevar a que el empleo de pautas posológicas estándares en el paciente crítico esté ligado a situaciones de infradosificación (ocasionando fracaso terapéutico y contribuyendo al desarrollo de resistencias) o sobredosificación (provocando efectos adversos y costes innecesarios).[11,12] De hecho, existe una amplia evidencia de que, en muchas ocasiones, los regímenes de dosificación convencionales no resultan óptimos para tratar infecciones en el paciente crítico.[15]

Además, las alteraciones anteriormente comentadas también afectar a la biodisponibilidad de los fármacos, por lo que en numerosas ocasiones resulta necesario recurrir a la vía de administración intravenosa, con el consiguiente aumento tanto del riesgo de infección nosocomial como de los costes que ello entraña.[13,41]

El problema de la resistencia antimicrobiana en el paciente crítico

En los últimos años, la resistencia a antibacterianos se ha convertido en un grave problema, debido a una disminución en el ritmo de desarrollo de nuevos antibióticos, al aumento de su consumo y al empleo de pautas posológicas infraterapéuticas.[42] Según datos de la *Food and Drug Administration* (FDA), entre 1960 y 1990 aconteció un aumento en el desarrollo de nuevos antibacterianos, que alcanzó su máximo en torno al año 2000, produciéndose a partir de entonces un importante descenso del mismo.[43] De forma paralela, el consumo de antibióticos a nivel ambulatorio se ha visto aumentado en los últimos años, hasta llegar a 22,4 Dosis Diaria Definida (DDD) por mil habitantes y día en 2015 en la Unión Europea.[44] Además, varios estudios realizados tanto fuera como dentro de Europa han puesto de manifiesto que habitualmente más del 40% de las prescripciones de antibióticos se consideran inapropiadas.[45]

La selección y propagación de cepas altamente resistentes, especialmente aquellas resistentes a antibióticos de última línea, como carbapenems, suponen un grave problema a nivel de salud pública, tanto desde un vista clínico como económico.

Se estima que actualmente 50.000 muertes anuales en Europa y Estados Unidos son debidas a infecciones por gérmenes multirresistentes. A nivel mundial, esta cifra se eleva a 700.000 si se consideran no sólo las infecciones bacterianas, sino también las debidas al Virus de la Inmunodeficiencia Humana (VIH), tuberculosis y malaria.[42,46]

En lo que respecta al ámbito económico, los hospitales de Europa y Estados Unidos gastan, en promedio, entre 10.000 y 40.000 € adicionales para tratar cada paciente infectado con bacterias resistentes.[46]

El problema del aumento en la incidencia de patógenos multirresistentes tiene más trascendencia en el ámbito de cuidados intensivos, debido a que la presión de

selección de mutantes resistentes y el riesgo de transmisión paciente-paciente son mayores.[47]

Además, aquellos pacientes infectados por bacterias multirresistentes son más propensos a desarrollar complicaciones y presentan mayor duración de la estancia hospitalaria y mayor morbi-mortalidad, con una probabilidad hasta 3 veces mayor de morir a causa de una infección.[46] Este tipo de infecciones conlleva un mal pronóstico en pacientes críticos.[47]

Por otro lado, los patógenos multirresistentes a menudo no producen una infección como tal, sino una colonización, constituyendo un reservorio oculto para la propagación de los mismos.[47] Esta situación también se ha visto asociada a un mayor riesgo de muerte, de duración de la hospitalización y de los costes sanitarios.[47]

Estos hallazgos ponen de manifiesto el considerable coste humano y económico que supone esta situación, lo que propició que el Ministerio de Sanidad, Servicios Sociales e Igualdad del Gobierno de España desarrollase en el año 2014 un plan de acción para reducir el riesgo de selección y diseminación de resistencias a antibióticos.[48] Dicho plan comprende 6 líneas estratégicas:

- Vigilancia del consumo de antibióticos y resistencias antimicrobianas
- Control de las resistencias bacterianas
- Identificación e impulso de medidas de prevención y tratamiento
- Definición de prioridades en materia de investigación
- Formación e información a profesionales sanitarios
- Comunicación y sensibilización de la población

Además, a partir de ese mismo año en España se puso en marcha el proyecto "Resistencia Zero", que planteaba el objetivo de reducir la incidencia acumulada de pacientes con infecciones adquiriridas en UCI debidas a patógenos multirresistentes en un 20%.[47]

Del mismo modo, en febrero de 2017, la OMS publicó un documento con los patógenos hacia los que debe dirigirse prioritariamente la investigación y desarrollo de nuevos

fármacos, estableciendo 3 categorías. Dentro de la categoría con máxima prioridad se encuentran: *Acinetobacter baumannii* resistente a carbapenems y *Pseudomonas aeruginosa* resistente a carbapenems, ambos bacilos no fermentadores, y enterobacterias resistentes a carbapenems y productoras de betalactamasas de espectro extendido (*Klebsiella pneumoniae*, *Escherichia coli* y *Enterobacter spp.*, entre otros).[49]

1.2.2. Papel del farmacéutico clínico en la optimización del tratamiento antiinfeccioso en el paciente crítico

Como ya se ha comentado, la cada vez más frecuente emergencia de patógenos multirresistentes, junto con la disminución en el desarrollo de nuevos antibacterianos, hace que la situación actual en relación al abordaje de las infecciones sea preocupante.[15]

El farmacéutico clínico posee conocimientos y habilidades que lo sitúan como un profesional garante de la calidad de la farmacoterapia de los pacientes, incluyendo el abordaje antiinfeccioso. La revisión elaborada por la OMS en 2014 acerca del papel del farmacéutico en relación al uso prudente de antimicrobianos sitúa al farmacéutico como profesional clave de la salud, con las habilidades y formación necesaria para contribuir a la reducción de resistencias antimicrobianas.[45]

Por ejemplo, el farmacéutico posee, desde sus estudios de pre-grado, formación profunda en farmacocinética y farmacodinamia. Y hay que considerar que considerar que los índices de actividad antimicrobiana son índices mixtos, constituidos por un parámetro farmacocinético (Concentración Máxima o Área Bajo la Curva concentración-tiempo) y un parámetro farmacodinámico (Concentración Mínima Inhibitoria).

Por otro lado, los antiinfecciosos constituyen uno de los grupos de medicamentos más frecuentemente involucrados en reacciones adversas a medicamentos, como se observa en el estudio de Baniasadi *et al.*[50], o relacionados con errores de medicación,

como observaron en su trabajo Karthikeyan *et al.*[51] Ambos trabajos confirman la relevancia de la contribución del farmacéutico en lo referente a la optimización de los tratamientos antimicrobianos.

En este sentido, como ya se ha comentado anteriormente, los pacientes críticos, debido a su mayor complejidad, constituyen uno de los grupos que más puede beneficiarse de la incorporación del farmacéutico al equipo multidisciplinar.

Por ello, con el objetivo de mejorar la calidad asistencial, el farmacéutico clínico se encuentra integrado en el equipo multidisciplinar del Área de Cuidados Críticos de la Clínica Universidad de Navarra desde el año 2002. En dicha área realiza intervenciones de las cuales, aproximadamente, un 33% corresponden a intervenciones relacionadas con tratamientos antimicrobianos.

El objetivo del farmacéutico clínico en relación a la optimización de antiinfecciosos en el paciente crítico es mejorar la efectividad y seguridad de los tratamientos, así como contribuir a la contención de la generación de nuevas resistencias antimicrobianas.

El papel del farmacéutico clínico en este área comprende la participación en el pase de visita, la revisión de la historia clínica electrónica y de los tratamientos antimicrobianos (existencia o no de alergias, pruebas analíticas, cultivos microbiológicos, tipo de antimicrobiano, pautas posológicas, duración de los tratamientos, detección de duplicidades, interacciones farmacológicas, *etc.*), así como la realización de recomendaciones específicas (optimización de las dosis, cambio de vía de administración, desescalado terapéutico, suspensión de tratamientos, adición de un nuevo antimicrobiano para obtener sinergia, *etc.*).

En concreto en relación a los tratamientos antimicrobianos en el paciente crítico, el farmacéutico contribuye de manera significativa al desescalado terapeútico de los tratamientos en base a cultivos microbiológicos tras el establecimiento de un tratamiento empírico inicial, a la terapia secuencial (disminuyendo el riesgo de infección nosocomial y los costes)[41], al cambio en el modo de administración de los fármacos (*p.ej*: recomendación de cambio de perfusión intermitente a perfusión

extendida en el caso de betalactámicos)[52], *etc.*, y tiene un papel relevante en la optimización de la pauta posológica de los antimicrobianos.

Como ya se ha expuesto anteriormente, los cambios que presenta el paciente crítico provocan que las pautas posológicas estándares de antimicrobianos no resulten idóneas. Del mismo modo, las alteraciones que presentan estos pacientes no son estáticas, sino que evolucionan con el tiempo,[13] por lo que, tras el establecimiento de la pauta inicial, la pauta posológica debe modificarse estrechamente para adaptarse a estos cambios, siendo el farmacéutico un profesional clave en la adaptación posológica.

Existe una clara evidencia de que la optimización de las pautas posológicas de los tratamientos antimicrobianos conlleva una mejoría en los resultados de los pacientes. De hecho, en estudios publicados que incluyen pacientes en estados de sepsis y shock séptico, las intervenciones que en mayor proporción mejoraron los resultados clínicos fueron las dirigidas a optimizar el tratamiento antimicrobiano.[11]

En este sentido, el farmacéutico, al estar integrado en el equipo del Área de Cuidados Críticos, se encuentra en contacto directo con los profesionales médicos en el momento de la prescripción, de modo que cuando se requiere, el farmacéutico actúa previo a que se administre la primera dosis del fármaco al paciente.

Del mismo modo, el farmacéutico clínico realiza diversas actividades complementarias, como proveer educación en relación a los medicamentos a los diferentes profesionales sanitarios, participar en comisiones implicadas en la utilización de antiinfecciosos a nivel hospitalario y formar parte de diferentes equipos multidisciplinares. En concreto, el farmacéutico clínico en la Clínica Universidad de Navarra, además de estar integrado en el equipo multidisciplinar del Área de Cuidados Críticos, forma parte del Programa de Optimización del uso de Antiinfecciosos (PROA) del hospital. Los PROAs se han constituido como una manera adicional efectiva de asegurar el uso prudente de los antimicrobianos. El papel del farmacéutico en los mismos resulta esencial, contribuyendo al uso racional de antibacterianos.[45] Cappelletty *et al.*[53] observaron un incremento en el uso inapropiado y en la duración de los tratamientos antimicrobianos

analizados, así como un aumento en el número de infecciones por *Clostridium difficile* durante la ausencia del farmacéutico en el PROA frente a cuando éste formaba parte del mismo. Por todo ello, en este momento resulta imprescindible el trabajo multidisciplinar y colaboración entre diferentes profesionales de la salud, con el objetivo de promover y contribuir a una prescripción eficaz y segura, en base a criterios tanto de efectividad como económicos.

La evidencia disponible hasta la fecha demuestra que las intervenciones farmacéuticas sobre antiinfecciosos en el ámbito hospitalario tienen un resultado positivo.[54] Ahora bien, el número de estudios que analiza resultados en salud dependientes de la actuación del farmacéutico clínico en un entorno tan complejo como el de las UCIs, es muy limitado.

Los pocos estudios comparativos que analizan el impacto clínico y económico de las intervenciones farmacéuticas en concreto sobre antiinfecciosos en pacientes críticos están realizados en Asia,[24,25] donde los protocolos de actuación y la regulación sanitaria difieren de los europeos, con las consecuencias que esto puede conllevar en los resultados clínicos y económicos obtenidos con las intervenciones farmacéuticas. Además, estos estudios fueron realizados en un contexto en el que no existían programas como el PROA en los hospitales, que realizan actividades complementarias a las llevadas a cabo por los farmacéuticos de los Servicios de Farmacia de los hospitales, entre los que se encuentran los farmacéuticos clínicos integrados en el equipo multidisciplinar de las UCIs.

Por todo ello, con objeto de optimizar el trabajo del equipo profesional implicado en el cuidado de los pacientes, resulta imprescindible evaluar el impacto de las intervenciones del farmacéutico clínico en las UCIs en Europa en el contexto de la práctica clínica.

Además, el farmacéutico clínico junto con el equipo médico de cuidados intensivos ha promovido y liderado iniciativas concretas dirigidas a la optimización de infecciones graves en el paciente crítico, como la utilización de antibioterapia inhalada añadida al tratamiento antiinfeccioso sistémico en pacientes con infecciones respiratorias.

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2. OBJETIVOS

Los objetivos del presente trabajo son:

1. Recoger y analizar la evidencia disponible en estudios comparativos respecto al impacto clínico y económico de las intervenciones del farmacéutico en relación con antimicrobianos en pacientes adultos en el ámbito hospitalario.

2. Analizar el impacto clínico y económico de las intervenciones sobre antiinfecciosos dirigidas a optimizar la farmacoterapia de los pacientes realizadas por el farmacéutico clínico integrado en el equipo asistencial del Área de Cuidados Críticos de la Clínica Universidad de Navarra. Identificar los Problemas Relacionados con Medicamentos y errores de medicación detectados por este farmacéutico relacionados con dichas intervenciones.

3. Evaluar el impacto clínico de una iniciativa concreta promovida y liderada por el farmacéutico clínico adscrito al Área de Cuidados Críticos con objeto de mejorar los resultados en los pacientes, en concreto la efectividad de la terapia antibiótica inhalatoria adicionada al tratamiento antiinfeccioso sistémico en el paciente crítico con infección respiratoria.

3. DESARROLLO DEL TRABAJO DE INVESTIGACIÓN

3.1. Evidence of clinical and economic impact of pharmacist interventions related to antimicrobials in the hospital setting

3.2. Clinical and economic impact of clinical pharmacist interventions regarding antimicrobials on critically ill patients

3.3. Effectiveness of inhaled antibiotic therapy in critically ill patients with respiratory infections

3.1. Evidence of clinical and economic impact of pharmacist interventions related to antimicrobials in the hospital setting

3.1.1. Abstract

Objectives

To review the literature regarding the clinical and economic impact of pharmacist interventions (PIs) related to antimicrobials in the hospital setting.

Materials and methods

A PubMed literature search from January 2003 to March 2016 was conducted using the terms *pharmacist* or clinical pharmacist** combined with *antimicrobial** or *antibiotic** or *anti-infective**. Comparative studies that assessed the clinical and/or economic impact of PIs on antimicrobials in the hospital setting were reviewed. Outcomes were classified as: treatment-related (TROs), clinical (COs), cost and microbiological outcomes (MOs). Acceptance of pharmacist recommendations by physicians was collected. PIs were grouped into patient-specific recommendations (PSRs), policy and education. Studies risk of bias was analyzed using *Cochrane´s tool.*

Results

Twenty-three studies were evaluated. All of them had high risk of bias. Design in most cases was uncontrolled before and after. PSRs were included in every study; five also included policy and four education. Significant impact of PI was found in 14 of the 18 studies (77.8%) that evaluated costs, 15 of the 20 (75.0%) that assessed TROs, 12 of the 22 (54.5%) that analyzed COs and 1 of the 2 (50.0%) that evaluated MOs. None of the studies found significant negative impact of PIs. It could not be concluded that adding other strategies to PSRs would improve results. Acceptance of recommendations varied from 70 to 97.5%.

Conclusions

Pharmacists improve TROs and COs, and decrease costs. Additional research with lower risk of bias is unlikely to change this conclusion. Future research should focus on identifying most efficient interventions.

3.1.2. Introduction

Infectious diseases and their treatments are a constant and growing concern in health policy.[1] In acute care hospitals, up to 52% of patients may receive an antibiotic during their stay.[2,3] It is estimated that between 30 and 50% of antibiotic treatments established in the hospital setting are inadequate and even suboptimal.[1] Inadequate use of anti-infectives contributes to the emergence and development of resistant organisms, leading to increased morbidity, mortality and healthcare costs. The increasing development of multidrug-resistant bacteria and the lack of new antibiotics against these pathogens make it necessary to implement specific actions that help optimize the use of antimicrobials.[1]

Several studies have demonstrated that pharmacist interventions (PIs) play a vital role in the optimization of antibiotic use,[4,5] resulting in improved care in inpatient settings.[3] A variety of strategies have been described to promote rational antibiotic use.[2] A clinical pharmacist who participates on ward rounds, reviewing prescriptions on a day-to-day basis can promote a rational and more efficient use of antimicrobials, shorten the course of the treatments, implement conversion from the intravenous to the oral administration route, decrease the overall number of antimicrobials administered, and give feedback and advice to the physician regarding the optimal choice.[3,6]

In their review, Von Gunten *et al.*[2] provided evidence of the clinical and economic benefits of pharmaceutical services with regard to the appropriate use of antibiotics. This review included articles published up to 2003, in which some studies analyzed pharmacists participation within a group of health care professionals, thereby making it impossible to determine the personal contribution of the pharmacists.

Nowadays, in many hospitals there is a Program for Optimizing the use of Antibiotics (PROA) conducted by teams in which there is also a pharmacist. However, PIs are complementary to interventions performed by these programs. PIs involve other aspects apart from those evaluated by the PROA, such as detection of interactions; therapeutic duplications; adverse drug events and/or medications errors; *etc*.

Until now, some reviews analyzing antimicrobial stewardship programs or other interventions to improve antibiotic prescribing practices in the hospital setting have been published.[7-10] However, there have been no reviews including studies that analyze the clinical and economic impact of interventions on antimicrobials conducted solely by pharmacists and carried out in the hospital setting. The effect of the interventions on antimicrobials performed solely by pharmacists, in many cases, in parallel with those developed by a multidisciplinary group has to be analyzed.

The aim of this study is to review the clinical and economic impact of PIs related to antimicrobials in an adult inpatient setting in order to summarize the evidence.

3.1.3. Materials and methods

Search strategy

A PubMed search was conducted to identify articles published from January 1, 2003 to March 11, 2016. The search strategy was designed using the following groups of words: (*pharmacist** OR *clinical pharmacist**) AND (*antimicrobial** OR *antibiotic** OR *anti-infective**).

Review process

The inclusion and exclusion criteria for the selection of articles are shown in Table 1.

Table 1. Inclusion and exclusion criteria for paper selection

Inclusion criteria	
Study design	Comparative studies
Language	English, Spanish or French
Participants	Adult patients admitted to a hospital or an emergency department
Setting	Interventions conducted in hospital
Interventions	Conducted by pharmacists regarding only antimicrobial agents
Comparison	Comparison between a group with pharmacist intervention and another without pharmacist intervention
Outcomes	Economical and/or clinical outcomes

Table 1 (continued)

Exclusion criteria	
Study design	-Non-comparative studies, letters to the editor, commentaries, news, reviews -Systematic reviews -Studies already included in review by Von Gunten *et al.*[2]
Participants	-Studies conducted exclusively with paediatric patients and/or diagnosed with cystic fibrosis
Setting	-Long-term care facilities, community pharmacies, primary care
Interventions	-Interventions targeted at drugs in general, even though they also involved antimicrobials -Interventions targeted at antiretroviral drugs, antimalarial drugs, antiviral therapy for hepatitis -Multidisciplinary team interventions, even though a pharmacist participated as part of the team
Comparison	Comparison between a generalist pharmacist and a pharmacist trained in antimicrobial stewardship

Note. Criteria were established following *PICO (participants, interventions, comparisons, and outcomes)* criteria.

First, each reference title was screened. Then abstracts of non-excluded papers were screened for eligibility against inclusion and exclusion criteria. The full text of all selected papers were read and selected similarly. References from reviewed articles were analyzed to identify other potential articles that could be included in the study if they fulfilled inclusion criteria.

Data collected from each study

The following characteristics of each study were retrieved: general information (first author and year of publication), study design (uncontrolled before and after study (UBA), controlled before and after study (CBA), observational controlled study based on surveys and databases (OCSD), controlled trial (CT), randomized controlled trial (RCT)), setting (country, hospital type, ward type), intervention description, patient characteristics, size of each group, age per group and outcomes (type of outcome, outcome variables, results by group and results of comparison test).

Quality Assessment of Individual Studies

The methodological quality of the studies was assessed according to the *Cochrane risk of bias tool*.[11] This is a domain-based evaluation in which critical assessments are made over seven separate domains: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting and other sources of bias. Domains were scored as high, low or unclear risk of bias. Literature search, data extraction and quality evaluation of the included studies were conducted by the main investigator; unclear cases were reviewed by two investigators and discussed until a consensus was reached.

Analysis of results

PIs were classified as patient-specific recommendations (PSRs), policy and/or education. PSRs were defined as interventions concerning patient-specific antimicrobial treatments, and included at least one of the following: recommendation to initiate or to discontinue antimicrobial therapy, promotion of rational use, proposal of dose or dosing interval modification, switching therapy, therapeutic drug monitoring (TDM) and ordering laboratory tests. The second type of PI, implementation of policies, consisted of the development of guidelines, protocols and/or specific programs for recommendations concerning antimicrobial use, dose and regarding switching therapy. The third type of PI, education, referred to providing educational sessions, feedback or delivering lectures on rational antimicrobial use to physicians and nurses.

Outcomes were categorized into: treatment-related outcomes (TROs), clinical outcomes (COs), cost and microbiological outcomes (MOs). TROs referred to different aspects regarding antimicrobial treatments. The following items were used to analyze the effect of PIs on TROs: duration of antimicrobial therapy, rate of appropriate duration of antimicrobial therapy, duration of intravenous treatment, rate of appropriate selection and use of antimicrobials, rate of appropriate dosing, dosing errors, time to intervention, time to effective antimicrobial prescription and/or rate of switching from intravenous to oral administration route. COs included results related to patients care. Variables used in the studies to quantify the effect of PIs on COs were:

length of hospital and Intensive Care Unit (ICU) stay, mortality, rate of postoperative infections, clinical success (used in one study[12] and defined as an improvement in temperature, white blood cell count and mechanical ventilation status), readmissions and rate of adverse drug reactions. Cost data were expressed in studies as cost of drugs in general, antibiotic cost, total hospitalization cost and ICU hospitalization cost. For the studies that found significant positive impact on costs, we calculated the percentage of decrease in costs with PIs versus without PIs. MOs included the rate of pathogen eradication, *Clostridium difficile* development and the rate of resistant isolates.

Results were tabulated. In order to identify PIs with impact on outcomes, the number of studies with a significant positive impact on at least one outcome variable was obtained. This result was classified by type of PI and by type of outcome.

A comparison of this result between different types of PIs was conducted by logistic regression and a comparison of the number of outcome variables with a significant positive impact between only PSR or a combination of strategies was performed using the *Mann-Whitney U* test.

3.1.4. Results

Study selection

The PubMed search identified 906 citations. All of them were screened for inclusion by reviewing their titles; 230 remained for a second screening on the abstract. A total of 73 were screened for full text review and 21 of them fulfilled inclusion criteria. Two articles were added from study references (Figure 1). Therefore, 23 studies were finally included in this review.

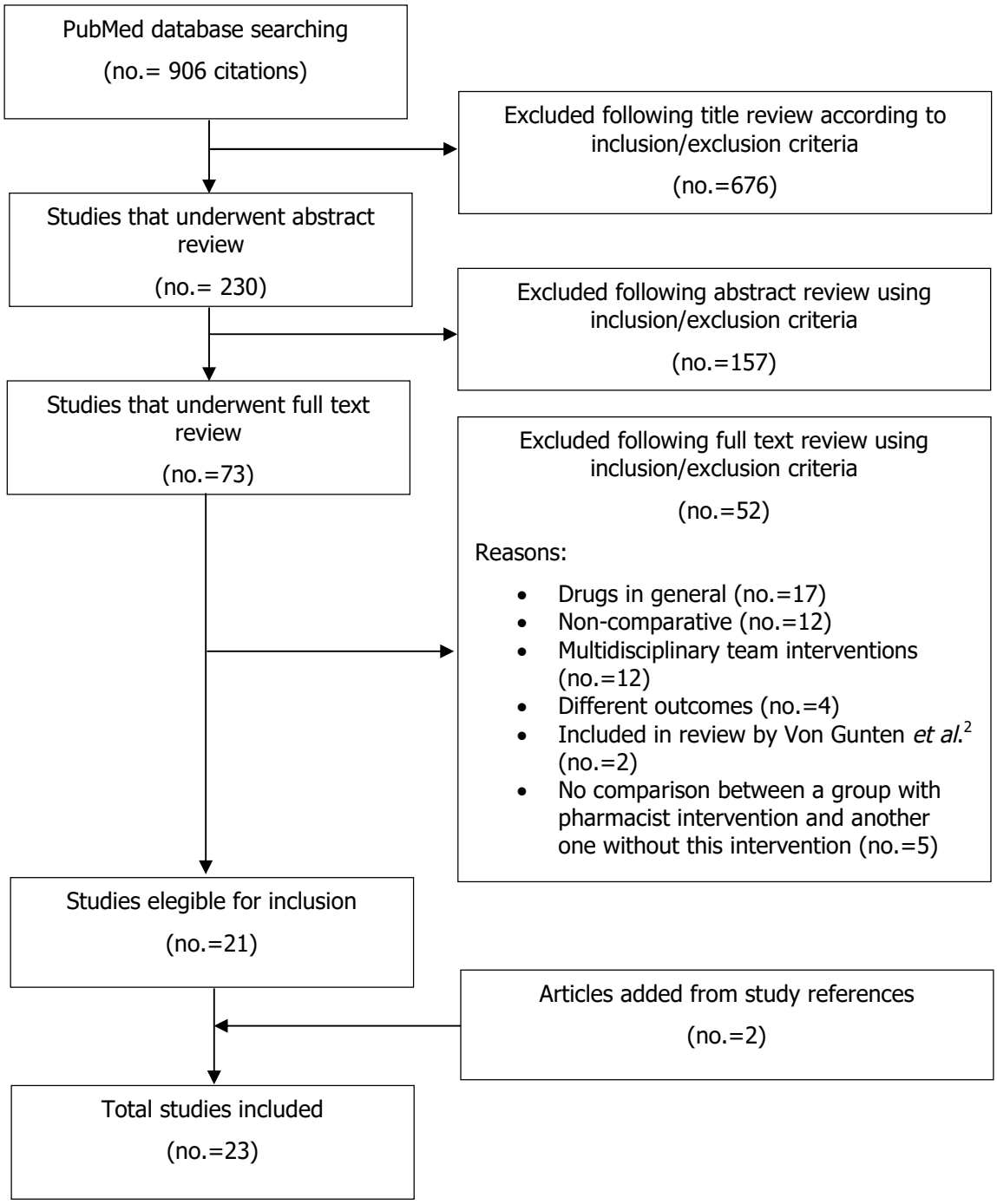

Figure 1. Flow diagram

Study characteristics

Characteristics of the 23 articles included in this review are summarized in Table 2.

Table 2. Characteristics of included studies

First author (Year)	Study design	Setting (country/ hospital type/ward)	Type of intervention	Interventions	Patient characteristics	Sample size per group	Age per group (years, mean (SD) (p value)
Davis (2016)[13]	UBA	**Country:** USA **Hospital:** Tertiary teaching **Ward:** Non-trauma emergency department	PSR	**INT:** Pharmacist performing daily culture review, informing and making recommendations to physicians. **PRE:** Nurse performing daily culture review, informing and making recommendations to physicians**.**	Patients with positive cultures from specimens obtained in the emergency department	**INT:** 30 **PRE:** 42	**INT:** 51.4 (22.1) **PRE:** 49.9 (20.3) (p=0.77)
Zhou (2016)[14]	UBA	**Country:** China **Hospital:** Tertiary teaching **Ward:** Cardiothoracic surgical	PSR+ Education	**INT:** Pharmacist participating in ward rounds and making drug treatment plans, communicating with surgeons, educational sessions, extracting medical records, assessing responsible use of antimicrobials and reporting their irrational use. **POST:** After discontinuation of all active pharmacist interventions (6 month period).	Patients who underwent cardiothoracic surgery and the surgical operation was clean or clean-contaminated	**INT:** 551 **PRE:** 412 **POST:** 156	**INT:** 55.6 (15.3) **PRE:** 54.8 (16.3) (p=0.46) **POST:** 56.8 (15.4) (p=0.54)
Marquis (2015)[15]	UBA	**Country:** USA **Hospital:** Tertiary academic medical centre **Ward:** All wards	PSR+Policy	**INT:** Pharmacist developing and implementing a pharmacist-driven vancomycin dosing guideline, recommending optimal vancomycin dosing for each patient.	Adult inpatients receiving intravenous vancomycin for >24 hours.	**INT:** 158 **PRE:** 161	**INT:** 49 (13.5) **PRE:** 49 (15.6) (p=0.99)
Tavakoli-Ardakani (2015)[16]	UBA	**Country:** Iran **Hospital:** Teaching hospital **Ward:** ICU and haematology-oncology	PSR	**INT:** Pharmacist reviewing medical charts and laboratory data, collecting data and assessing appropriateness of vancomycin use, contacting physicians.	Patients with intravenous vancomycin	**INT:** 82 **PRE:** 77	**INT:** 49 (20.24) **PRE:** 44 (16.7) (p=NR)

Table 2 (continued)

First author (Year)	Study design	Setting (country/ hospital type/ward)	Type of intervention	Interventions	Patient characteristics	Sample size per group	Age per group (years, mean (SD) (p value)
Wang (2015)[5]	UBA	**Country:** China **Hospital:** Tertiary hospital **Ward:** Department of gynaecology and obstetrics	PSR+ Education	**INT:** Pharmacist providing education to obstetricians, real-time monitoring of clinical records, judging the appropriateness of prophylactic antibiotic use, communicating with the obstetricians and making recommendations, providing feedback to the hospital administration.	Adult patients admitted to the maternity ward and undergoing elective caesarean section	**INT:** 197 **PRE:** 197	**INT:** 27.73 (3.86) **PRE:** 27.03 (3.65) (p=0.067)
Zhou (2015)[17]	UBA	**Country:** China **Hospital:** Tertiary hospital **Ward:** Department of urology	PSR+ Education +Policy	**INT1:** First year of pharmacist interventions. Pharmacist participating in antibiotic management group, carrying out analysis of antibiotic use, providing feedback, compiling rules, guidelines, making posters for promoting the responsible use of antimicrobials. **INT2:** Second year of pharmacist interventions. Pharmacist participating in ward rounds, assessing the use of antimicrobials, delivering lectures on antimicrobials, participating in consultations. **INT3:** Third year of pharmacist interventions. Antibiotic use in clean-contaminated operations.	Patients who underwent clean urological operations	**INT1:** 3,641 **INT2:** 4,372 **INT3:** 4,697 **PRE:** 3,043	**INT1:** 52.85 (13.48) **INT2:** 48.91 (13.56) **INT3:** 51.10 (13.14) **PRE:** 51.31 (13.27) (p=NS)[a]
Jiang (2014)[18]	UBA	**Country:** China **Hospital:** University- affiliated hospital **Ward:** ICU	PSR	**INT:** Pharmacist making antimicrobial dosing adjustment interventions and recommendations.	Critically ill adult patients receiving continuous venovenous hemodiafiltration and receiving at least 1 antimicrobial therapy	**INT:** 93 **PRE:** 87	**INT:** 62.0 (18.4) **PRE:** 59.3 (20.6) (p=0.53)

Table 2 (continued)

First author (Year)	Study design	Setting (country/ hospital type/ward)	Type of intervention	Interventions	Patient characteristics	Sample size per group	Age per group (years, mean (SD) (p value)
Reed (2014)[19]	UBA	**Country:** USA **Hospital:** Teaching hospital **Ward:** All wards	PSR	**INT:** Pharmacist reviewing charts and contacting physicians to make recommendations.	Adult patients with *Candida* spp. isolated from a blood culture	**INT:** 88 **PRE:** 85	**INT:** 56 (46-67)[b] **PRE:** 54 (48-66)[b] (p=0.66)
Yagi (2014)[20]	CT	**Country:** Japan **Hospital:** Medical school hospital **Ward:** All wards	PSR	**INT:** Pharmacological intervention for meropenem treatment: initiating meropenem administration, suggesting increase in quantity and number of doses, suggesting adjustment of dosage interval.	Patients with serious infections who were successfully treated with meropenem A: CrCl>50 ml/min B: CrCl≤50 ml/min	**INT-A:** 171 **CTRL-A:** 176 **INT-B:** 103 **CTRL-B:** 97	**INT-A:** 64.3 (18.3) **CTRL-A:** 66.3 (17.5) (p=0.30) **INT-B:** 75.9 (10.8) **CTRL-B:** 74.7 (11.4) (p=0.44)
Zhang (2014)[21]	UBA	**Country:** China **Hospital:** Tertiary hospital **Ward:** Department of Urological surgery	PSR	**INT:** Pharmacist monitoring medical records, controlling prescription of prophylactic antibiotics and communicating with surgeons.	Patients undergoing either clean or clean-contaminated surgery	**INT:** 196 **PRE:** 174	**INT:** 50.43 (14.48) **PRE:** 52.61 (14.35) (p=NS)
Jiang (2013)[22]	UBA	**Country:** China **Hospital:** University-affiliated hospital **Ward:** ICU	PSR	**INT:** Pharmacist assessing patients, adjusting dosage of antimicrobial drugs and making recommendations.	Adult septic patients receiving continuous renal replacement therapy and at least 1 antimicrobial drug	**INT:** 73 **PRE:** 71	**INT:** 57.9 (15.4) **PRE:** 62.3 (17.0) (p=0.28)

Table 2 (continued)

First author (Year)	Study design	Setting (country/ hospital type/ward)	Type of intervention	Interventions	Patient characteristics	Sample size per group	Age per group (years, mean (SD) (p value)
Yen (2012)[23]	UBA	**Country:** Taiwan **Hospital:** Tertiary teaching hospital **Ward:** All wards	PSR+Policy	**INT:** Pharmacist developing clinical criteria protocol to identify candidates for iv to po conversion, evaluating patients	Adult patients admitted to the general wards and prescribed with iv levofloxacin	**INT:** 37 **PRE:** 42	**INT:** 73.9 (17.2) **PRE:** 78.0 (15.4) (p=0.247)
Dunn (2011)[24]	CBA	**Country:** Ireland **Hospital:** Academic hospital **Ward:** All wards	PSR+Policy	**INT:** Application of stickers to the drug chart highlighting that the patient was being treated with iv antimicrobials, application of guidelines to the drug chart with criteria for iv to po switch, contacting with junior doctors.	Patients who were prescribed an intravenous antimicrobial during the first 4 days of admission	**INT:** 72 **CTRL:** 44 **PRE:** 73 **CTRL-PRE:** 47	**INT:** 62[c] **CTRL:** 62[c] (p=NS) **PRE:** 74[c] **CTRL-PRE:** 65[c] (p=NS)
Grill (2011)[3]	UBA	**Country:** Germany **Hospital:** University hospital **Ward:** Surgical department	PSR	**INT:** Pharmacist reviewing prescription charts, taking part in ward rounds and giving advice, including TDM.	Adult patients admitted to surgical units and receiving antimicrobial therapy	**INT:** 321 **PRE:** 317	**INT:** 60.9 (14.9) **PRE:** 61.8 (14.9) (p= 0.459)
Randolph (2011)[25]	UBA	**Country:** USA **Hospital:** Medical centre **Ward:** Emergency department	PSR	**INT:** Case review by pharmacist **PRE:** Case review by physician	Patients admitted to the emergency department with culture samples	**INT:** 2,361 **PRE:** 2,278	NR

Table 2 (continued)

First author (Year)	Study design	Setting (country/ hospital type/ward)	Type of intervention	Interventions	Patient characteristics	Sample size per group	Age per group (years, mean (SD) (p value)
Shen (2011)[4]	RCT	**Country:** China **Hospital:** Tertiary hospital **Ward:** 2 independent respiratory wards	PSR	**INT:** Pharmacist as part of the treating team, communicating with the physician and making recommendations.	Inpatients diagnosed with respiratory tract infections	**INT:** 176 **CTRL:** 178	**INT:** 60.3 (18.1) **CTRL:** 59.8 (17.6) (p=0.34)
Toth (2010)[26]	UBA	**Country:** USA **Hospital:** Tertiary hospital **Ward:** Internal medicine and surgery floor	PSR+ Education	**INT:** Pharmacist establishing practice with the medical team, monitoring of cultures and antimicrobial therapy, suggesting changes and providing education.	Patients admitted to the internal medicine or surgery floor receiving any one or any combination of the following antibiotics: antipseudomonal beta-lactam, vancomycin, fluoroquinolone, linezolid, aminoglycoside.	**INT:** 80 **PRE:** 80	**TOTAL:** 59 (47-77)[b] (p=NS)[d]
Bond (2007)[27]	OCSD	**Country:** USA **Hospital:** 806 acute care, general-medical surgical hospitals, acute care paediatric hospitals **Ward:** All wards	PSR	**INT:** Hospitals with pharmacist ordering laboratory tests, initiating drug therapy, or adjusting drug dosage to obtain desired therapeutic outcome. **CTRL:** Hospitals without pharmacist management	Hospitalized surgical Medicare patients receiving antimicrobial prophylaxis	**INT:** 56,874 **CTRL:** 185,830	NR
Bond (2005)[28]	OCSD	**Country:** USA **Hospital:** 961 acute care, general medical-surgical hospitals, acute care paediatric hospitals **Ward:** All wards	PSR	**INT:** Hospitals with pharmacist ordering laboratory tests, initiating drug therapy, or adjusting drug dosage to obtain desired therapeutic outcome. **CTRL:** Hospitals without pharmacist management.	Hospitalized Medicare patients who had diagnoses indicating that they were probably treated with an aminoglycoside or vancomycin therapy	**INT:** 106,364 **CTRL:** 92,718	NR

Table 2 (continued)

First author (Year)	Study design	Setting (country/ hospital type/ward)	Type of intervention	Interventions	Patient characteristics	Sample size per group	Age per group (years, mean (SD) (p value)
Davis (2005)[12]	UBA	**Country:** USA **Hospital:** University-affiliated trauma centre **Ward:** All wards	PSR	**INT1:** Pharmacist switching therapy from iv B-lactam±macrolide to po levofloxacin. **INT2:** Pharmacist initiating automatic conversion from iv moxifloxacin to po moxifloxacin.	Adult patients with a diagnosis of community-acquired pneumonia	**INT1:** 81 **INT2:** 91 **PRE:** 79	**INT1:** 49.9[c] **INT2:** 52.5[c] **PRE:** 50.42[c] (p=NS)[a]
Ho (2005)[29]	UBA	**Country:** Canada **Hospital:** General teaching hospital **Ward:** All wards	PSR	**INT:** Pharmacist-managed Dosage Form Conversion Service: reviewing drug and health reports, writing orders for the po regimen, monitoring clinical progress and medication tolerability. **PRE:** iv-po Step-down Program without pharmacist intervention.	Patients receiving iv ciprofloxacin	**INT:** 100 **PRE:** 100	**INT:** 63 (16-91)[e] **PRE:** 57 (17-93)[e] (p=NS)
Von Gunten (2005)[30]	RCT	**Country:** Switzerland **Hospital:** 3 secondary- care hospitals **Ward:** General medical wards and ICU	PSR+Policy	**INT:** Implementation of guidelines with reinforcement by a clinical pharmacist. Pharmacist reviewing medical charts and participating in medical rounds, making recommendations to physicians. **CTRL1:** No intervention. **CTRL2:** Implementation of guidelines without clinical pharmacist.	Patients receiving antibiotic therapy	**INT:** 200 **CTRL1:** 200 **CTRL2:** 200 **PRE:** 200 **CTRL1-PRE:** 200 **CTRL2-PRE:** 200	**INT:** 74.0 (18-98)[e] **CTRL1:** 73.7 (14-95)[e] **CTRL2:** 71.7 (16-103)[e] (p= 0.428)[f] **PRE:** 69.4 (19-97)[e] **CTRL1-PRE:** 72.1 (14-94)[e] **CTRL2-PRE:** 76.6 (15-97)[e] (p= 0.078)[g]

Table 2 (continued)

First author (Year)	Study design	Setting (country/ hospital type/ward)	Type of intervention	Interventions	Patient characteristics	Sample size per group	Age per group (years, mean (SD) (p value)
Pinteño Blanco (2004)[31]	UBA	**Country:** Spain **Hospital:** Tertiary hospital **Ward:** All wards	PSR	**INT:** Pharmacist sending a note with benefits and recommendations of sequential therapy and contacting physicians.	Patients admitted to areas with unit dose system who were treated with iv quinolones (levofloxacin (A) or ciprofloxacin (B)) for at least 48 hours	**INT-A:** 40 **PRE-A:** 36 **INT-B:** 34 **PRE-B:** 36	**INT-A:** 67.0 (17.1) **PRE-A:** 71.4 (14.4) (p=0.141) **INT-B:** 61.0 (18.7) **PRE-B:** 61.9 (15.8) (p=0.883)

CBA: controlled before and after study; CrCl: creatinine clearance; CT: controlled trial; CTRL: control group simultaneous in time with intervention group. Refers to standard care without pharmacist intervention, unless otherwise stated; CTRL-PRE: control group simultaneous in time with pre-intervention group (PRE); ICU: intensive care unit; INT: during intervention; iv: intravenous; NR: not reported; NS: not significant (p>0.05); OCSD: observational controlled study based on surveys and databases; p: probability of the comparison versus intervention, unless otherwise stated, extracted from the publication; po: oral; POST: after the intervention; PRE: before the intervention. Refers to standard care without pharmacist intervention, unless otherwise stated; PSR: patient-specific recommendation; RCT: randomized controlled trial; SD: standard deviation; spp.: species; TDM: therapeutic drug monitoring; UBA: uncontrolled before and after study; USA: United States of America. Some abbreviations are followed by a number (*e.g.* 1,2,3) indicating the level of intervention or control explained in the "interventions" column; and followed by letters (*e.g.* A,B) indicating different subgroups defined in the "patient characteristics" column.

[a]p refers to the probability of the comparison between all groups.
[b]Age is indicated as median (interquartile range) in years
[c]Age is indicated as median in years
[d]p refers to the probability of the comparison between INT and PRE group.
[e]Age is indicated as median (range) in years
[f]p refers to the probability of the comparison between the groups during intervention.
[g]p refers to the probability of the comparison between the groups before the intervention.

Most of the studies had a UBA design (n=17). The other studies were 2 OCSD, 2 RCT, 1 CBA and 1 CT. The majority of the studies were published in 2010 or later (n=17). Included studies covered different continents: Europe (n=4), Asia (n=10) and America (n=9). All the included studies except 3 were single-centre (n=20). Ten studies included all hospital wards, whereas the other ones (n=13) focused only on specific wards. Of these, 5 studies only evaluated surgical wards[3,5,14,17,21] and 2 studies were only developed in the ICU.[18,22]

In studies comparing non-simultaneous groups, data for different groups were collected during similar periods of time (except for 3 studies[15,17,29]), ranging from 2 months to 1 year. The number of included patients varied considerably among the studies, which ranged from 72[13] to 242,704[27] patients. No significant differences were found in demographic or baseline characteristics between compared groups in 11 studies.[13,17,18,20-24,26,29,31] Significant differences were found in 1 or 2 baseline characteristics in 8 studies,[3-5,12,14,15,19,30] diagnosis being the most frequently different;[3,4,12,30] baseline characteristics were not described in 3 studies;[25,27,28] and one additional study did not report results of statistical comparison between groups.[16]

Quality assessment of individual studies

The quality of the studies was poor, with only two RCT,[4,30] one CBA[24] and one CT.[20]

None of the included studies used blinding of participants and personnel, none reported on allocation concealment and only one study reported a clear randomization sequence, with all of them resulting in a high risk of bias (appendix 1).

Results of Individual Studies: Pharmacist Interventions (PIs) and Outcome Measurements

Types of PIs of each study are shown in Table 2. Different types of PIs were often combined. PSR was a strategy used in every study, implementation of policies was present in 5 papers,[15,17,23,24,30] and education was used in 4 cases.[5,14,17,26]

Results of individual studies are summarized in Table 3

Table 3. Outcomes reported in each study

First author (Year)	Results						
	Type of outcome	**Outcome variable**	**Results by group**			**Comparison test**	
Davis (2016)[13]			**PRE**	**INT**		**p**	
	*TRO*s	Interventions on positive cultures that required an intervention (%)	50	80		**0.01**	
		Time to intervention (days), mean (SD)	3.4 (1.9)	3.5 (1.2)		0.81	
Zhou (2016)[14]			**PRE**	**INT**	**POST**	**p(PRE vs. INT)**	**p(INT vs. POST)**
	*TRO*s	Duration of antibiotic prophylaxis >48h (%)	96.5	64.0	63.8	**<0.001**	0.96
		Unnecesary antibiotic combination (%)	23.4	0	1.3	**<0.001**	0.21
		Rational antibiotic selection (%)	42.1	95.1	97.1	**<0.001**	0.43
		Unnecessary replacement of drugs (%)	17.5	6.5	--	**<0.001**	NA
	*CO*s	Surgical site infections (%)	3.5	1.2	1.4	**0.02**	>0.99
		Length of hospital stay (days), mean (SD)	23.3 (8.9)	20.9 (8.9)	21.6 (8.8)	**<0.001**	0.54
	Cost	Cost of prophylactic antibiotics (USD), mean (SD)	232.1 (199.0)	64.7 (44.44)	67.2 (52.6)	**<0.001**	0.67
		Mean incremental cost (USD)		13.7		NA	
		Benefit-to-cost ratio		11.3:1		NA	
	*MO*s	Resistant isolates (%)				**<0.001** for some bacteria	

Table 3 (continued)

First author (Year)	Results				
	Type of outcome	**Outcome variable**	**Results by group**		**Comparison test**
Marquis (2015)[15]			**PRE**	**INT**	**p**
	*TRO*s	Patients who receive optimal vancomycin dosing (%)	40.4	96.8	**<0.001**
		Patients with dose increase within 24 hours (%)	8	58	**<0.001**
		Length of vancomycin therapy (days), mean (SD)	10.0 (4.5)	8.4 (4.2)	**0.003**
	*CO*s	Length of hospital stay	NR	NR	NS
		Length of ICU stay	NR	NR	NS
		Nephrotoxicity (%)	8.7	3.2	**0.03**
		Ototoxicity (%)	0	0	NA
Tavakoli-Ardakani (2015)[16]			**PRE**	**INT**	**p**
	*TRO*s	Appropriate initiation of vancomycin therapy (%)	38.96	59.76	**0.009**
		Appropriate duration of vancomycin therapy (%)	83.33	77.55	0.54
		Vancomycin therapy stopped following discussion with physician (%)	--	50	NA
		Appropriate dosing regimen of vancomycin therapy (%)	54.55	65.85	0.5
		Dosing regimen adjusted following discussion (%)	--	30.77	NA
	*CO*s	Infusion related adverse drug reactions (%)	22.08	10.98	0.06

Table 3 (continued)

First author (Year)	Results				
	Type of outcome	**Outcome variable**	**Results by group**		**Comparison test**
Wang (2015)[5]			**PRE**	**INT**	**p**
	TROs	Duration of prophylaxis antibiotic (days), mean	4.05	1.86	**<0.001**
		Correct choice of prophylaxis antibiotic (%)	4.06	94.42	NR
		Correct choice of prophylaxis antibiotic + correct dose (%)	3.55	93.91	NR
		Correct choice of prophylaxis antibiotic + correct dose + correct timing (%)	2.54	92.39	NR
		Correct choice of prophylaxis antibiotic + correct dose + correct timing + correct duration (%)	0.00	19.29	**<0.001**
	COs	Length of hospitalization (days), mean	6.21	6.25	0.536
	Cost	Total cost of prophylactic antibiotics (USD)	71,694	3,669.76	NR
		Cost of hospitalization (USD/patient), mean	1,903.26	1,529.35	**<0.001**
		Total drug cost (USD/patient), mean	780.36	546.16	**<0.001**
		Prophylactic antibiotic cost (USD/patient), mean	363.93	18.63	**<0.001**
		Cost of prophylactic antibiotic usage (USD/patient-day), mean	60.35	2.96	**<0.001**
		Benefit-to-cost ratio	27.23:1		NA

Table 3 (continued)

First author (Year)	Results								
	Type of outcome	**Outcome variable**	**Results by group**				**Comparison test**		
Zhou (2015)[17]			**PRE**	**INT1**	**INT2**	**INT3**	**p(PRE vs. INT1)**	**p(INT1vs. INT2)**	**p(INT2vs. INT3**
	TROs	Use of antibiotic profilaxis (%)	100	100	9	7	NA	**0.000**	0.656
		Antibiotic prescriptions that met indications for prophylaxis, timing, duration, antibiotic combination and antibiotic selection (%)	22	9	50	80	0.131	**0.024**	0.689
		Duration of antibiotic treatment (days), mean (SD)	3.92 (1.59)	3.17 (1.07)	1.33 (0.52)	2.00 (1.41)	**0.008**	**0.000**	0.525
		Antibiotic combination (%)	44	6	0	0	**0.000**	1.000	NA
	COs	Length of hospitalization (days), average	11.95	10.43	9.12	8.58	NR		
	Cost	Total drug cost (USD/patient), average	803.86	708.97	614.62	632.91	NR		
		Cost of antibiotics (USD/patient), average	338.0	209.53	105.25	91.06	NR		
Jiang (2014)[18]			**PRE**	**INT**			**p**		
	TROs	Number of antimicrobials use in ICU, mean (SD)	1.9 (1.1)	2.1 (1.0)			0.31		
		Duration of antimicrobial therapy (days), mean (SD)	8.5 (5.6)	7.9 (4.9)			0.42		
	COs	Mortality in ICU (%)	32.2	35.5			0.57		
		Length of ICU stay (days), mean (SD)	9.3 (7.7)	8.5 (7.0)			0.46		
		Antimicrobial related adverse drug events (%)	29.9	11.8			**0.002**		
	Cost	Antimicrobial drug cost (€/case), mean (SD)	2,164.3 (1,158.0)	1,555.5 (824.5)			**0.043**		
		Total drug cost (€/case), mean (SD)	3,669.3 (2,660.3)	2,812.9 (2,143.9)			**0.038**		
		ICU hospitalization cost (€/case), mean (SD)	8,613.0 (6,922.3)	6,975.3 (6,515.0)			**0.029**		
		Acceptance of recommendations (%)	87.5				NA		

Table 3 (continued)

First author (Year)	Results				
	Type of outcome	**Outcome variable**	**Results by group**		**Comparison test**
Reed (2014)[19]			**PRE**	**INT**	**p**
	*TRO*s	Time from Gram stain to effective antifungal prescription in working hours (hours), median (IQ range)	9.2 (0.3-21.4)	0.1 (0-1.3)	**0.01**
		Time from Gram stain to effective antifungal therapy hang time in working hours (hours), median (IQ range)	13.5 (2.0-25.9)	1.3 (0-3.2)	**0.04**
		Effective antifungal therapy prescription (%)	88	99	**0.008**
		In-hospital duration of antifungal therapy in patients with effective therapy (days), median (IQ range)	9 (6-15)	11 (7-15)	0.56
	*CO*s	Overall length of stay (days), median (IQ range)	15 (9-28)	19 (11.5-29.5)	0.37
		Infection-related length of stay (days), median (IQ range)	10 (7-15.5)	11 (7-17)	0.68
		In-hospital mortality (%)	19	30	0.11
	Cost	Hospital costs during candidemia (USD), median (IQ range)	25,697 (15,654-42,870)	31,457 (16,399-83,649)	0.25
		Total hospital costs (USD), median (IQ range)	44,616 (25,713-98,234)	56,875 (28,696-113,753)	0.29

Table 3 (continued)

First author (Year)	Results							
	Type of outcome	**Outcome variable**	**Results by group**				**Comparison test**	
Yagi (2014)[20]			**A**		**B**		**p(A)**	**p(B)**
			CTRL	**INT**	**CTRL**	**INT**		
	*TRO*s	Duration of meropenem treatment (days), mean (SD)	9.4 (5.4)	7.4 (3.7)	9.4 (6.9)	8.3 (5.1)	**<0.01**	0.17
	*CO*s	Incidence of liver dysfunction due to meropenem (%)	14.8	11.1	28.9	18.5	0.74	**0.02**
		Incidence of renal dysfunction due to meropenem (%)	12.5	7.6	17.5	14.6	0.13	0.57
		Incidence of convulsions due to meropenem (%)	0.57	0.59	2.06	0.97	0.98	0.61
	Cost	Antimicrobial drug cost (USD/3 years)	**(CTRL-A)+(CTRL-B):** 102,220 **(INT-A)+(INT-B):** 84,730				**0.04**	
		Acceptance of interventions (%)	74.3-80.4				NA	
Zhang (2014)[21]			**PRE**		**INT**		**p**	
	*TRO*s	Duration of antibiotics prophylaxis (days), mean	7.58		2.91		**<0.001**	
		Number of antibiotics used, mean	1.73		1.28		**<0.001**	
		Prophylactic antibiotic usage (%)	100.00		76.68		**<0.001**	
		Prophylactic antibiotics not required but administered (%)	48.54		35.23		**0.004**	
		Unnecessary broad spectrum and expensive antibiotic use (%)	59.09		25.00		**<0.001**	
		Unnecessary replacement of antibiotics (%)	54.55		27.50		**<0.001**	
		Unnecessary combination of antibiotics (%)	14.77		7.50		NS	
		Unnecessarily high doses of 2nd generation cephalosporins or aztreonam (%)	66.22		79.49		NS	

Table 3 (continued)

First author (Year)	Results				
	Type of outcome	**Outcome variable**	**Results by group**		**Comparison test**
Zhang (2014)[21]			**PRE**	**INT**	**p**
	TROs	First postoperative dose administered during an inappropriate time frame (%)	0.00	2.50	NS
		Unnecessary prolonged duration of prophylaxis (%)	100.00	75.00	**<0.001**
		Correct choice of antibiotic administration (%)	22.72	68.75	**<0.001**
		Correct choice and dose of antibiotic administration (%)	6.82	7.50	NS
		Correct choice, dose and timing of antibiotic administration (%)	6.82	7.50	NS
		Correct choice, dose, timing and duration of antibiotic administration (%)	0.00	0.00	NA
	COs	Postoperative infection rates (%)	1.72	1.53	NS
	Cost	Total hospitalization cost (USD), mean	4,141.26	4,134.24	NS
		Total drug cost (USD), mean	1,606.31	1,526.17	NS
		Cost of antibiotics (USD), mean	338.59	98.95	**<0.001**
		Benefit-to-cost ratio	18.79:1		NA

Table 3 (continued)

First author (Year)	Results				
	Type of outcome	**Outcome variable**	**Results by group**		**Comparison test**
Jiang (2013)[22]			**PRE**	**INT**	**p**
	*TRO*s	Number of antimicrobials use in ICU, mean (SD)	2.2 (1.0)	2.5 (1.0)	0.41
		Number of dosing errors	194 in 71 patients	54 in 73 patients	**<0.001**
		Vancomycin levels reaching desired trough value (%)	31 in 47 patients (66.0)	47 in 56 patients (83.9)	**<0.001**
	*CO*s	ICU mortality (%)	52.9	47.9	0.56
		Length of ICU stay (days), mean (SD)	10.7 (11.1)	7.7 (8.3)	**0.037**
		Number of antimicrobial adverse drug events	19	8	**0.048**
	Cost	ICU antimicrobial cost (USD/admission), mean (SD)	5,129 (6,096)	3,809 (3,691)	**0.046**
		ICU hospitalization cost (USD/admission), mean (SD)	13,463 (12,045)	9,938 (8,811)	**0.038**
		Acceptance of interventions (%)	91.8		NA
Yen (2012)[23]			**PRE**	**INT**	**p**
	*TRO*s	iv/po ratio, mean (SD)	3.0 (0.6)	2.1 (0.6)	**0.032**
		Length iv antibiotic treatment (days), mean (SD)	8.3 (3.8)	6.6 (4.4)	0.075
		Length of antibiotic treatment (days), mean (SD)	9.9 (4.3)	9.3 (5.3)	0.575
	*CO*s	Length of hospital stay (days), mean (SD)	27.2 (18.5)	16.1 (9.3)	**0.001**
	Cost	Cost of antibiotics during hospitalization (USD/patient), mean (SD)	568.9 (262.9)	449.0 (266.4)	**0.044**
		Total inpatient expenditures (USD/patient), mean (SD)	6,096.5 (5,164.0)	3,649.6 (3,740.4)	**0.017**

Table 3 (continued)

First author (Year)	Results							
	Type of outcome	**Outcome variable**	**Results by group**				**Comparison test**	
Dunn (2011)[24]			**CTRL-PRE**	**PRE**	**CTRL**	**INT**	**p(CTRL-PRE vs. PRE)**	**p(CTRL vs. INT)**
	*TRO*s	Duration of iv antimicrobial treatment (hours), median	80	88	96	72	0.599	**0.02**
		IV courses switched to po (%)	70.0	84.3	85.2	83.7	NR	NR
		IV courses switched to po on appropriate day (%)	56.7	50.6	55.5	71.7	0.257	**0.017**
	*CO*s	Length of hospital stay (days), median	11.5	9	11	10	NS	NS
		30-day mortality rate	NR				NS	NS
	Cost	Antibiotic cost (€/patient), mean	INT: €6.41 less compared to PRE; CTRL: €1.69 less compared to CTRL-PRE				NR	
Grill (2011)[3]			**PRE**		**INT**		**p**	
	*TRO*s	Length of antimicrobial therapy (days), adjusted incidence rate ratio for INT vs. CTRL (CI95%)	11		10		**<0.0001**	
			Adjusted incidence rate ratio: 0.88; CI95%: 0.84-0.93					
		Length of iv therapy (days), mean	10		8		**p<0.0001** adjusted for covariates	
		Administrations switched from iv to po (%)	10		18		**0.001**	
		Time to switch	NR (shorter in INT vs. CTRL)				**0.001**	
		Useless combination therapy	NR				0.18	
		Length of useless combination therapy	NR (shorter in INT vs. CTRL)				**<0.0001**	
	*CO*s	Length of hospital stay (days), median (range)	18 (3-220)		19 (3-130)		0.857	
		Readmission within 6 weeks after discharge (%)	NR		NR		NS	
	Cost	Cost of antimicrobials per patient, mean	16% lower in INT vs. CTRL				**0.04**	
		Acceptance of interventions (%)	70				NA	

Table 3 (continued)

First author (Year)	Results				
	Type of outcome	**Outcome variable**	**Results by group**		**Comparison test**
Randolph (2011)[25]			**PRE**	**INT**	**p**
	*CO*s	Patients that experience an unplanned readmission to the emergency department (%)	19	7	**<0.001**
		Treatment failure as reason for unplanned readmission (%)	19.7	12.7	**<0.001**
		Noncompliance due to cost as reason for unplanned readmission (%)	14.6	10.9	**<0.001**
		Noncomplicance for any reason other than cost as reason for unplanned readmission (%)	39.8	40.6	**<0.001**
		Allergy to medication as reason for unplanned readmission (%)	9.0	2.4	**<0.001**
		Adverse drug reaction as reason for unplanned readmission (%)	13.9	30.3	0.08
Shen (2011)[4]			**CTRL**	**INT**	**p**
	*TRO*s	Score of inappropriate indication for antibiotic use	18	8	NR
		Score of inappropriate choice of antibiotics	98	21	NR
		Score of inappropriate dosage of antibiotics	19	5	NR
		Score of inappropriate dosing schedule of antibiotics	74	71	NR
		Score of inappropriate duration of antibiotic treatments	66	23	NR
		Score of inappropriate timely conversion from iv to oral administration route	101	55	NR
	*CO*s	Length of hospital stay (days), mean (SD)	15.8 (6.0)	14.2 (6.2)	**0.03**

Table 3 (continued)

First author (Year)	Results				
	Type of outcome	**Outcome variable**	**Results by group**		**Comparison test**
Shen (2011)[4]			**CTRL**	**INT**	**p**
	Cost	Total cost of hospitalization (USD/patient), mean (SD)	1,729.6 (773.7)	1,442.3 (684.9)	**<0.001**
		Total cost of antibiotics (USD/patient), mean (SD)	943.9 (412.0)	832.0 (373.0)	**0.01**
Toth (2010)[26]			**PRE**	**INT**	**p**
	*TRO*s	Compliance with all quality indicators (documentation of treatment rationale, and appropriateness of cultures, empirical therapy and de-escalation) (%)	16	54	**<0.001**
		Duration of antimicrobial therapy (days), median	8	6	0.1
	*CO*s	Mortality	NR		NS
		Length of hospital stay	NR		NS
	*MO*s	Pathogen eradication (%)	90	98	0.09
		Clostridium difficile development (%)	10	5	0.23
		Acceptance of interventions (%)	91		NA
Bond (2007)[27]			**CTRL**	**INT**	**p**
	*CO*s	Mortality (%)	4.06	2.67	**<0.0001**
		Length of hospital stay (days), mean (SD)	8.85 (9.16)	8.03 (8.16)	**<0.0001**
		Postoperative infections (%)	1.72	1.13	**<0.001**
	Cost	Medicare charges (USD/case), mean (SD)	32,560 (37,199)	31,580 (35,768)	**<0.0001**
		Drug charges (USD/case), mean (SD)	4,321 (8,593)	4,029 (8,271)	**0.005**

Table 3 (continued)

First author (Year)	Results					
	Type of outcome	**Outcome variable**	**Results by group**			**Comparison test**
Bond (2005)[28]			**CTRL**	**INT**		**p**
	*CO*s	Mortality (%)	17.96	16.83		**<0.0001**
		Mortality in patients with complications (%)	27.88	25.31		**<0.0001**
		Length of hospital stay (days), mean (SD)	12.98 (18.66)	11.56 (18.73)		**<0.0001**
		Hearing loss (%)	6.75	4.61		**<0.0001**
		Renal impairment (%)	34.52	25.77		**<0.0001**
	Cost	Medicare charges (USD/case), mean (SD)	25,623 (46,455)	24,105 (39,411)		**<0.0001**
		Drug charges (USD/case), mean (SD)	4,976 (10,070)	4,601 (10,855)		**<0.0001**
Davis (2005)[12]			**PRE**	**INT1**	**INT2**	**p**[a]
	*TRO*s	Length of iv therapy (days), mean	3.89	3.63	2.67	**0.005**
		Excess length of iv therapy (days), mean	2.14	0.96	0.35	**<0.001**
	*CO*s	Number of adverse events possibly or probably attributed to study medications	0	0	0	NA
		Clinical success of treatment on day 3 of therapy (%)	83.4	84.0	94.5	**0.045**
		Clinical success of treatment on day 7 of therapy (%)	96.2	92.6	95.6	NS
		Clinical success of treatment at the end of therapy (%)	98.7	98.8	97.8	NS
		Infection-related length of stay (days), mean	4.23	4.57	4.39	0.846
		Infection-related readmission within 30 days after discharge (%)	3.8	4.9	4.4	NS

Table 3 (continued)

First author (Year)	Results					
	Type of outcome	**Outcome variable**	**Results by group**			**Comparison test**
Davis (2005)[12]			**PRE**	**INT1**	**INT2**	**p**[a]
	Cost	Cost of iv antibacterials (USD/patient)	222	215	108	**<0.0001**
		Antibacterial acquisition costs (USD/patient)	230	233	119	**<0.0001**
		Costs included other antibacterial-related costs (TDM, administration…) (USD/patient)	306	314	145	**<0.0001**
		Hospitalization cost (USD/patient)	3,409	3,631	3,547	NS
Ho (2005)[29]			**PRE**	**INT**		**p**
	*TRO*s	Lenght of hospital stay (days), median (range)	12 (1-84)	17 (1-165)		NS
		iv:po ciprofloxacin use ratio	3.03	3.48		0.2830
		iv to po conversion rate (% by iv treatment courses)	27	23		0.73
		Proportion of inappropriate iv ciprofloxacin doses (%)	47	36		**0.0005**
		Proportion of pharmacist-preventable inappropriate iv ciprofloxacin doses (%)	47	32		**0.0026**
	Cost	Proportional cost avoidance associated with inappropriate iv ciprofloxacin doses (%)	43	34		**0.001**
		Proportional pharmacist-preventable cost avoidance associated with inappropriate iv ciprofloxacin use (%)	20	11		**0.001**

Table 3 (continued)

First author (Year)	Results										
	Type of outcome	Outcome variable	Results by group						Comparison test		
			CTRL1-PRE	CTRL1	CTRL2-PRE	CTRL2	PRE	INT	p(CTRL1-PRE vs. CTRL1)	p(CTRL2-PRE vs. CTRL2)	p(PRE vs. INT)
Von Gunten (2005)[30]	*TRO*s	Duration of iv antibiotics (days), median (IQ range)	2.0 (2.0)	2.5 (2.0)	5.0 (4.0)	5.0 (4.5)	4.0 (2.0)	4.0 (2.0)	0.230	0.203	0.533
		Duration of all antibiotics (days), median (IQ range)	6.0 (5.0)	8.0 (5.0)	8.0 (7.0)	8.0 (7.0)	7.0 (5.0)	7.0 (5.0)	**0.002**	0.183	0.753
		Adherence to guidelines				56%		72%		**0.002**[b]	
	*CO*s	Length of stay (days), median (IQ range)	9.0 (6.0)	10.0 (7.0)	10.0 (9.0)	10.0 (9.0)	10.0 (9.0)	11.0 (8.0)	**0.013**	0.058	0.322
	Cost	Cost of antibiotics (€), median (IQ range)	27.5 (53.5)	37.4 (63.1)	68.4 (103.5)	82.3 (118.3)	45.9 (67.6)	46.0 (101.4)	**0.011**	0.099	0.391
		Global cost (€), median (IQ range)	51.9 (84.5)	65.4 (85.3)	128.2 (184.1)	149.9 (196.5)	80.8 (110.4)	83.3 (158.6)	**0.014**	0.085	0.520

Table 3 (continued)

First author (Year)	Results							
	Type of outcome	**Outcome variable**	**Results by group**				**Comparison test**	
			PRE-A	**INT-A**	**PRE-B**	**INT-B**	**p(A)**	**p(B)**
Pinteño Blanco (2004)[31]	*TRO*s	Length of iv quinolone therapy (days), mean (SD)	6.4 (2.7)	3.2 (0.9)	6.6 (4.3)	3.2 (1.0)	**<0.001**	**<0.001**
		Conversion day (days), mean (SD)	6.3 (2.0)	4.1 (0.2)	7.0 (3.3)	4.1 (0.7)	**<0.001**	**<0.001**
		Length of quinolone therapy (days), mean (SD)	9.2 (3.1)	8.4 (3.0)	10.6 (7.7)	9.2 (6.6)	0.122	0.430
	*CO*s	Length of hospital stay (days), mean (SD)	14.6 (6.4)	11.4 (5.6)	23.8 (16.8)	17.8 (16.2)	**0.012**	**0.010**
	Cost	Quinolone acquisition cost (€/patient), mean (SD)	199.5 (78.5)	109.9 (27.9)	269.0 (211.1)	153.3 (66.8)	**<0.001**	**0.009**
		Acceptance of interventions (%)	97.5		85.3		NA	

CO: clinical outcome; CI95%: 95% confidence interval; CTRL: control group simultaneous in time with intervention group. Refers to standard care without pharmacist intervention, unless otherwise stated in Table 2; CTRL-PRE: control group simultaneous in time with pre-intervention group (PRE); ICU: intensive care unit; INT: during intervention; IQ range: interquartile range; iv: intravenous; MO: microbiological outcome; NA: not applicable; NR: not reported; NS: not significant (p>0.05); p: probability of the comparison versus intervention, unless otherwise stated, extracted from the publication; po: oral; POST: after the intervention; PRE: before the intervention. Refers to standard care without pharmacist intervention, unless otherwise stated in Table 2; SD: standard deviation; TDM: Therapeutic Drug Monitoring; TRO: treatment-related outcome; USD: United States Dollars; vs.: versus; €: euro. Some abbreviations are followed by a number (*e.g.* 1,2,3) indicating the level of intervention or control explained in Table 2; and followed by letters (*e.g.* A,B) indicating different subgroups defined in Table 2.

[a]p refers to the probability of the comparison between all groups.
[b]p refers to the probability of the comparison between CTRL2 and INT.

Measured outcomes included:

1) Treatment-related outcomes (TROs):

TROs were evaluated in 20 studies.[3-5,12-24,26,29-31] The most frequently analyzed variable was the duration of antimicrobial treatments (in 13 studies).[3,5,14,15,17-21,23,26,30,31] Fifteen of the twenty studies (75.0%) that assessed TROs showed a significant impact of PIs on at least one TRO.[3,5,12,14-17,19-22,24,26,30,31]

2) Clinical outcomes (COs):

COs were evaluated in 22 studies.[3-5,12,14-31] The most frequently analyzed variable was the length of hospital stay (in 16 studies).[3-5,12,14,15,17,19,23,24,26-31] Twelve of the 22 studies (54.5%) that assessed COs showed a significant impact of PIs on at least one CO.[4,12,14,15,18,20,22,23,25,27,28,31]

3) Cost:

Cost data were evaluated in 18 studies.[3-5,12,14,17-24,27-31] Antibiotic cost was the most frequently analyzed variable (in 15 studies).[3-5,12,14,17,18,20-24,29-31] Fourteen of the 18 studies (77.8%) that assessed costs found a significant impact of PIs on at least one outcome variable.[3-5,12,14,18,20-23,27-29,31]

For the studies that found significant positive impact on costs, we calculated the percentage of decrease in costs with PIs versus without PIs from the results obtained in Table 3. We observed a decrease up to 30% in the cost of drugs in general,[5] a decrease up to 95% on antibiotic cost,[5] up to 40% on total hospitalization cost[23] and up to 26% on the ICU hospitalization cost.[22]

4) Microbiological outcomes (MOs):

MOs were analyzed in 2 studies.[14,26] Only one of the 2 studies (50.0%) that assessed MOs found a significant impact of PIs.[14]

None of the studies found PIs to have a statistically significant negative impact on TROs, COs, costs, or MOs.

The analysis of the number of studies by type of intervention and the number of studies with significant positive impact by measured outcome variables are shown in Table 4 and Appendix 2.

Table 4. Number of studies by type of intervention and number of studies with significant positive impact by analyzed outcome variables

Type of intervention	**Studies, no.**				
PSR only	15				
Policy+PSR	4				
Education+PSR	3				
Policy+Education+PSR	1				
Outcome variables	**Studies, no.[a]**	**Studies with significant positive impact[b]**		**Studies that do not analyze significance**	
		Studies, no.	**%**	**Studies, no.**	**%**
TROs:					
1) Duration of antimicrobial therapy	13	7[c]	53.8	0	0.0
2) Appropriate duration of antimicrobial therapy	5	2	40.0	1	20.0
3) Duration of intravenous treatment	6	4	66.7	0	0.0
4) Appropriate selection and use of antimicrobials	10	7[c]	70.0	1	10.0
5) Appropriate dosing	7	4	57.1	1	14.3
6) Dosing errors	1	1	100.0	0	0.0
7) Time to intervention and/or time to effective antimicrobial prescription	2	1	50.0	0	0.0
8) Rate of switching from intravenous to oral administration route	3	1	33.3	1	33.3
Total:	**20**	**15**	**75.0**	2	10.0
COs:					
1) Length of hospital stay	16	6	37.5	1	6.3
2) Length of ICU stay	3	1	33.3	0	0.0
3) Mortality	7	2	28.6	0	0.0
4) Rate of postoperative infections	3	2	66.7	0	0.0
5) Early clinical success	1	1[d]	100.0	0	0.0
6) Readmissions	3	1	33.3	0	0.0
7) Adverse drug reactions	7	5[e]	71.4	0	0.0
Total:	**22**	**12**	**54.5**	1	4.5
Costs:					
1) Cost of drugs in general	6	4	66.7	1	16.7
2) Antibiotic cost	15	12	80.0	2	13.3
3) Total hospitalization cost	9	5	55.6	0	0.0
4) ICU hospitalization cost	2	2	100.0	0	0.0
Total:	**18**	**14**	**77.8**	2	11.1
MOs:					
1) Pathogen eradication	1	0	0.0	0	0.0
2) *Clostridium difficile* development	1	0	0.0	0	0.0

Table 4 (continued)

Outcome variables	Studies, no.[a]	Studies with significant positive impact[b]		Studies that do not analyze significance	
		Studies, no.	%	Studies, no.	%
MOs:					
3) Resistant isolates	1	1[d]	100.0	0	0.0
Total:	**2**	**1**	**50.0**	0	0.0

CO: clinical outcome; ICU: intensive care unit; MO: microbiological outcome; no.: number of studies; PSR: patient-specific recommendation; TRO: treatment-related outcome

[a]Total number of studies, including studies that reported significant positive impact with pharmacist intervention versus with no pharmacist intervention, those that analyzed significance but did not obtain significant positive impact, and those that did not analyze significance. None of the studies that did not obtain significant positive impact reported statistically significant negative impact.
[b]Significant positive impact with pharmacist intervention versus with no pharmacist intervention.
[c]One of the studies showed significant positive impact in part.
[d]The study showed significant positive impact in part.
[e]Two of the studies showed significant positive impact in part.

According to the type of PI, PSRs were presented in every study that showed significant impact of PIs on TROs (15 studies), COs (12 studies), costs (14 studies) and MOs (1 study). Education was presented in 26.7% of the studies with a significant impact on TROs, in 8.3% of the studies with a significant impact on COs, in 14.3% of the studies with a significant impact on costs and in 100% of the studies with a significant impact on MOs. Policy was presented in 26.7% of the studies with a significant impact on TROs, in 16.7% of studies with a significant impact on COs and in 7.1% of the studies with a significant impact on costs (appendix 3).

With regard to combinations of different types of PIs, it was not demonstrated that adding another strategy to PSRs increases the chances of having a significant positive impact on at least one outcome variable neither the number of outcome variables with significant positive impact (appendixes 4a and 4b), although the number of studies is small and therefore, the confidence intervals for odds ratios are wide.

Acceptance of recommendations made by pharmacists was described in 6 studies,[3,18,20,22,26,31] obtaining rates from 70 to 97.5%.

3.1.5. Discussion

Our review revealed that pharmacist interventions to optimize anti-infective treatments were associated with positive impact. PIs had a significant positive impact in 80% of the studies evaluating costs, 75% of the papers that studied TROs, 55% of the studies that analyzed COs and 50% of the studies that measured MOs. Most of the studies included in this review analyzed COs, TROs and costs. Only 2 of the included studies analyzed MOs.

In future studies, COs have to be included as the main outcome variables. TROs may be easier to measure than COs, but demonstrating the impact of PIs on COs has more clinical relevance. TROs have to be evaluated in a very objective way in order to be valid and to be associated with a better quality of patient care. For example, the duration of an antibiotic therapy may not be a good outcome measure, because even if it is an objective outcome it may not always be related to better care. Other outcomes such as appropriate antibiotic selection, unnecessary replacement of drugs, and so on, may not be objective measures, unless they are analyzed in an unbiased manner. Therefore, in general, COs are more valid than TROs, and every study has to include at least some CO measures.

With regard to COs, PIs had a significant impact on some relevant outcome measures such as decreasing surgical site infections[14] and post-operative infections,[27] nephrotoxicity[15,28] and other antimicrobial-related adverse effects,[18,20,22,28] length of hospital and/or ICU stay,[4,14,22,23,27,28,31] unplanned readmissions,[25] mortality,[27,28] or early clinical success.[12] The PIs related to these important outcomes were communicating and making treatment adjustments and/or recommendations to physicians involving specific patients,[4,12,14,15,18,20,22,25,27,28,31] developing guidelines and protocols[15,23] and providing educational sessions,[14] pharmacist being part of the treating team[4] and participating in ward rounds.[14]

Our review did not document any significant negative impact of PIs on measured outcomes. As other authors have suggested,[32] studies with negative results are less likely to be published.

With respect to cost outcomes, we found that PIs led to a decrease on antibiotic cost up to 95%[5] and to a decrease on total hospitalization cost up to 40%[23] in some studies.

Benefit-to-cost ratio in the three studies that analyzed this item was 11.3:1[14], 18.79:1[21] and 27.23:1[5] thereby showing that PIs provided financial benefits. Nonetheless, the size of cost avoidance obtained in the studies was likely to depend on the setting in which the evaluation was conducted and the intensity of care. These economic impact evaluations had some limitations because most of them focused on costs related only to antimicrobials. Incorporation of other costs such as pharmacist salary, cost associated with the PIs, cost of required programs and educational material, savings from avoiding adverse events, as well as savings derived from a faster clinical cure would produce a better estimate of the true economic impact of the intervention.

The impact of PIs on microbiological data was only evaluated in 2 studies. Changes in the rate of bacterial resistances are difficult to link solely to PIs, as many other factors can have a certain degree of influence, such as changes in infection control procedures and rotation of antimicrobials.

Studies with better methodologies, RCT, CBA and CT,[4,20,24,30] found significant impact of PIs on the following outcomes: TROs (*e.g.* reduction in the duration of antimicrobial therapy from 9.4 to 7.4 days[20] and in the duration of intravenous treatment from 4 to 3 days,[24] and increase in the adherence to guidelines from 56% to 72%[30]), COs (*e.g.* reduction in length of hospital stay from 15.8 to 14.2 days,[4] reduction in incidence of antimicrobial related liver disfunction from 28.9% to 18.5%[20]) and costs (*e.g.* reduction in antimicrobial drug cost in 3 years from 102,220 $ to 84,730 $[20] an in the total cost of hospitalization from 1,729.6 $ to 1,442.3 $[4]).

Only one study analyzed outcomes after the intervention had ended.[14] The study included patients admitted to a cardiothoracic surgical ward of a hospital in China and interventions consisted of a clinical pharmacist participating in ward rounds and communicating with surgeons when necessary, providing educational sessions, assessing the use of prophylactic antimicrobials and reporting their irrational use to leadership. The results obtained in the intervention period were maintained after

discontinuation of the active interventions during the 6-month post-intervention period. However, it cannot be concluded that this could be accomplished for a longer period of time.

With respect to the type of strategy used, PSR was the most prevalent type of PI. Eight studies included a combination of 2 or 3 types of strategies, making it difficult to determine the effect of each type of intervention separately. PSR is a type of PI with impact on TROs, COs, costs and MOs and it has not been demonstrated that adding other strategies would increase this impact. PSRs generally consisted of a pharmacist participating in ward rounds, reviewing patient charts and communicating patient specific recommendations (*e.g.* dose adjustments, switching from intravenous to oral route) directly to physicians.

In the study by Zhou *et al.*,[17] in which different levels of intervention were analyzed (in the first year of PIs, the pharmacist provided guidelines and rules; in the second year of PIs, pharmacist participated in ward rounds, *etc.*), participation in ward rounds and assessing the use of antimicrobials provided significant results in the rate of antibiotic use, in the rate of antibiotic prescriptions that met indications for prophylaxis, timing, duration, antibiotic combination and antibiotic selection, and in the duration of antimicrobial treatment compared to only providing rules or guidelines. Therefore, according to this study, it seems that PSRs have some impact in addition to that of rules and guidelines.

In a study by Davis *et al.*,[13] in which PI was compared with nurse intervention, a significant impact of PIs was found on the rate of interventions on positive cultures that required an intervention (80% vs. 50%, p=0.01), demonstrating that the pharmacists intervened in more cases than the nurses. This could be expected due to the difference in roles and knowledge about drugs between nurses and pharmacists.

The main limitation of this analysis is the difficulty that exists when trying to come to general and objective conclusions, due to the wide variability between studies and their limited methodological quality. The current state of evidence is mostly limited to uncontrolled before and after studies conducted in single centres without a well-designed control group. Selection and performance bias were the most frequent source

of bias. This failed to distinguish the real intervention effect from the confounding factors. Blinding of participants and personnel is difficult to develop in this context; in most of the included studies, the evaluators were the same people who carried out the interventions. Controlled studies, blinded data analysts, objective definitions of outcomes and a proper statistical analysis adjusting by confounders would have reduced the risk of bias and would permit to obtain a better estimate of the real effect of PIs. However, these strategies are difficult to conduct in this context and, despite these limitations, the general conclusion would probably be similar, as most studies coincide in a positive impact of PIs.

Inclusion of patient views regarding the role of pharmacists as part of the healthcare team as well as the impact of PIs on quality of life measures would complement the analysis.

Many of the studies were developed in Asia and North America, and the application of these results to other settings has to be done with caution. Health practice, funding or regulation of health services vary between different countries and this may influence economic and clinical outcomes.

3.1.6. Conclusions

The impact of pharmacist interventions related to antimicrobials has been evaluated. Pharmacists integrated in the healthcare team providing patient-specific recommendations improve treatment-related and clinical outcomes, and decrease costs. It cannot be concluded that adding other type of strategy, such as policy or education, to patient-specific recommendations would improve results obtained with this strategy. The published studies had limitations in their methodology. However, additional research with lower risk of bias is unlikely to change this conclusion. Future research should focus on identifying those pharmacist interventions that are more efficient.

3.1.7. References

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3.1.8. Supplementary data

Appendix 1. Risk of bias of included studies by source of bias

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Davis (2016)[13]	-	-	-	+	+	+	+
Zhou (2016)[14]	-	-	-	+	+	+	+
Marquis (2015)[15]	-	-	-	?	+	+	?
Tavakoli-Ardakani (2015)[16]	-	-	-	-	+	+	?
Wang (2015)[5]	-	-	-	+	+	+	+
Zhou (2015)[17]	-	-	-	-	+	+	+
Jiang (2014)[18]	-	-	-	+	+	+	+
Reed (2014)[19]	-	-	-	-	+	+	?
Yagi (2014)[20]	-	-	-	-	+	+	+
Zhang (2014)[21]	-	-	-	+	+	+	+
Jiang (2013)[22]	-	-	-	+	+	+	+
Yen (2012)[23]	-	-	-	+	+	+	+

Appendix 1 (continued)

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Dunn (2011)[24]	-	?	-	+	+	-	+
Grill (2011)[3]	-	-	-	-	+	+	+
Randolph (2011)[25]	-	-	-	-	+	+	-
Shen (2011)[4]	?	?	-	+	+	+	+
Toth (2010)[26]	-	-	-	-	+	+	?
Bond (2007)[27]	-	-	-	-	?	+	+
Bond (2005)[28]	-	-	-	-	?	+	+
Davis (2005)[12]	-	-	-	+	+	+	+
Ho (2005)[29]	+	-	-	+	+	+	+
Von Gunten (2005)[30]	?	-	-	+	+	+	+
Pinteño Blanco (2004)[31]	-	-	-	-	+	+	?

- high risk of bias
+ low risk of bias
? unclear risk of bias

Appendix 2. Number of studies by type of intervention and number of studies with significant positive impact by analyzed outcome variables with the references[a]

Type of intervention	**Studies, no.**				
PSR only	15[3,4,12,13,16,18-22,25,27-29,31]				
Policy+PSR	4[15,23,24,30]				
Education+PSR	3[5,14,26]				
Policy+Education+PSR	1[17]				
Outcomes	**Studies, no.[a]**	**Studies with significant positive impact[b]**		**Studies that do not analyze significance**	
		Studies, no.	**%**	**Studies, no.**	**%**
TROs:					
1) Duration of antimicrobial therapy	13[3,5,14,15,17-21,23,26,30,31]	7[c3,5,14,15,17,20,21]	53.8	0	0.0
2) Appropriate duration of antimicrobial therapy	5[4,5,16,17,21]	2[5,21]	40.0	1[4]	20.0
3) Duration of intravenous treatment	6[3,12,23,24,30,31]	4[3,12,24,31]	66.7	0	0.0
4) Appropriate selection and use of antimicrobials	10[3-5,14,16,17,19,21,26,30]	7[c5,14,16,19,21,26,30]	70.0	1[4]	10.0
5) Appropriate dosing	7[4,5,15,16,19,21,22]	4[5,15,19,22]	57.1	1[4]	14.3
6) Dosing errors	1[22]	1[22]	100.0	0	0.0
7) Time to intervention and/or time to effective antimicrobial prescription	2[13,19]	1[19]	50.0	0	0.0
8) Rate of switching from intravenous to oral route	3[3,24,29]	1[3]	33.3	1[24]	33.3
Total:	**20[3-5,12-24,26,29-31]**	**15[3,5,12,14-17,19-22,24,26,30,31]**	**75.0**	2[4,24]	10.0
COs:					
1) Length of hospital stay	16[3-5,12,14,15,17,19,23,24,26-31]	6[4,14,23,27,28,31]	37.5	1[17]	6.3
2) Length of ICU stay	3[15,18,22]	1[22]	33.3	0	0.0
3) Mortality	7[18,19,22,24,26-28]	2[27,28]	28.6	0	0.0
4) Rate of postoperative infections	3[14,21,27]	2[14,27]	66.7	0	0.0
5) Early clinical success	1[12]	1[d12]	100.0	0	0.0
6) Readmissions	3[3,12,25]	1[25]	33.3	0	0.0
7) Adverse drug reactions	7[12,15,16,18,20,22,28]	5[e15,18,20,22,28]	71.4	0	0.0
Total:	**22[3-5,12,14-31]**	**12[4,12,14,15,18,20,22,23,25,27,28,31]**	**54.5**	1[17]	4.5

Appendix 2 (continued)

Outcomes	Studies, no.[a]	Studies with significant positive impact[b]		Studies that do not analyze significance	
		Studies, no.	%	Studies, no.	%
Costs:					
1) Cost of drugs in general	6[5,17,18,21,27,28]	4[5,18,27,28]	66.7	1[17]	16.7
2) Antibiotic cost	15[3-5,12,14,17,18,20-24,29-31]	12[3-5,12,14,18,20-23,29,31]	80.0	2[17,24]	13.3
3) Total hospitalization cost	9[4,5,12,19,21,23,27,28,30]	5[4,5,23,27,28]	55.6	0	0.0
4) ICU hospitalization cost	2[18,22]	2[18,22]	100.0	0	0.0
Total:	**18[3-5,12,14,17-24,27-31]**	**14[3-5,12,14,18,20-23,27-29,31]**	**77.8**	2[17,24]	11.1
MOs:					
1) Pathogen eradication	1[26]	0	0.0	0	0.0
2) *Clostridium difficile* development	1[26]	0	0.0	0	0.0
3) Incidence of resistant isolates	1[14]	1[d14]	100.0	0	0.0
Total:	**2[14,26]**	**1[14]**	**50.0**	0	0.0

CO: clinical outcome; ICU: intensive care unit; MO: microbiological outcome; no.: number of studies; PSR: patient-specific recommendation; TRO: treatment-related outcome

[a]Total number of studies, including studies that reported significant positive impact with pharmacist intervention versus with no pharmacist intervention, those that analyzed significance but did not obtain significant positive impact, and those that did not analyze significance data. None of the studies that did not obtain significant positive impact reported statistically significant negative impact.
[b]Significant positive impact with pharmacist intervention versus with no pharmacist intervention.
[c]One of the studies showed significant positive impact in part.
[d]The study showed significant positive impact in part.
[e]Two of the studies showed significant positive impact in part.

Appendix 3. Type of interventions in the studies with significant positive impact on different outcomes

Outcome	Studies with significant positive impact on at least one outcome variable	Type of intervention	% of each type of intervention
*TRO*s	Zhou (2016)[14]	PSR+Education	-PSR: 100.0% (15/15) -Education: 26.7% (4/15) -Policy: 26.7% (4/15)
	Marquis (2015)[15]	PSR+Policy	
	Tavakoli-Ardakani (2015)[16]	PSR	
	Wang (2015)[5]	PSR+Education	
	Zhou (2015)[17]	PSR+Education+Policy	
	Reed (2014)[19]	PSR	
	Yagi (2014)[20]	PSR	
	Zhang (2014)[21]	PSR	
	Jiang (2013)[22]	PSR	
	Dunn (2011)[24]	PSR+Policy	
	Grill (2011)[3]	PSR	
	Toth (2010)[26]	PSR+Education	
	Davis (2005)[12]	PSR	
	Von Gunten (2005)[30]	PSR+Policy	
	Pinteño Blanco (2004)[31]	PSR	
*CO*s	Zhou (2016)[14]	PSR+Education	-PSR: 100.0% (12/12) -Education: 8.3% (1/12) -Policy: 16.7% (2/12)
	Marquis (2015)[15]	PSR+Policy	
	Jiang (2014)[18]	PSR	
	Yagi (2014)[20]	PSR	
	Jiang (2013)[22]	PSR	
	Yen (2012)[23]	PSR+Policy	
	Randolph (2011)[25]	PSR	
	Shen (2011)[4]	PSR	
	Bond (2007)[27]	PSR	
	Bond (2005)[28]	PSR	
	Davis (2005)[12]	PSR	
	Pinteño Blanco (2004)[31]	PSR	
Costs	Zhou (2016)[14]	PSR+Education	-PSR: 100.0% (14/14) -Education: 14.3% (2/14) -Policy: 7.1% (1/14)
	Wang (2015)[5]	PSR+Education	
	Jiang (2014)[18]	PSR	
	Yagi (2014)[20]	PSR	
	Zhang (2014)[21]	PSR	
	Jiang (2013)[22]	PSR	
	Yen (2012)[23]	PSR+Policy	
	Grill (2011)[3]	PSR	
	Shen (2011)[4]	PSR	
	Bond (2007)[27]	PSR	
	Bond (2005)[28]	PSR	
	Davis (2005)[12]	PSR	
	Ho (2005)[29]	PSR	
	Pinteño Blanco (2004)[31]	PSR	
*MO*s	Zhou (2016)[14]	PSR+Education	-PSR: 100.0% (1/1) -Education: 100.0% (1/1)

CO: clinical outcome; MO: microbiological outcome; PSR: patient-specific recommendation; TRO: treatment-related outcome

Appendix 4a. Impact of different combinations of pharmacist interventions on having significant positive impact on at least one outcome variable

Type of outcome	Results	Studies, no.					OR (CI95%)[b]
		PSR only	PSR+ Policy	PSR+ Education	PSR+ Education+ Policy	PSR+ (Education or Policy or both)[a]	PSR+(Education or Policy or both) vs. PSR only
*TRO*s	Significant positive impact on at least one outcome variable	8	3	3	1	**7**	**2.63 (0.22-31.35)**
	No significant impact	3	1	--	--	1	
	Significance not analyzed	1	--	--	--	--	
	Total	12	4	3	1	8	
*CO*s	Significant positive impact on at least one outcome variable	9	2	1	--	**3**	**0.42 (0.07-2.66)**
	No significant impact	5	2	2	--	4	
	Significance not analyzed	--	--	--	1	1	
	Total	14	4	3	1	8	
Cost	Significant positive impact on at least one outcome variable	11	1	2	--	**3**	**0.27 (0.01-5.77)**
	No significant impact	1	1	--	--	1	
	Significance not analyzed	--	1	--	1	2	
	Total	12	3	2	1	6	
*MO*s	Significant positive impact on at least one outcome variable	--	--	1	--	**1**	**NA**
	No significant impact	--	--	1	--	1	
	Significance not analyzed	--	--	--	--		
	Total	0	0	2	0	2	

CI95%: 95% confidence interval; CO: clinical outcome; MO: microbiological outcome; NA: not applicable; no.: number of studies; OR: Odds ratio; PSR: patient-specific recommendation; TRO: treatment-related outcome; vs.: versus

[a]Calculated as the sum of the following columns: (PSR+Policy), (PSR+Education) and (PSR+Education+Policy).
[b]Odds ratio of the combination of PSR+(Education+Policy or both) versus PSR only.

Appendix 4b. Impact of different combinations of pharmacist interventions on the number of outcome variables with significant positive impact

Type of outcome	Results	PSR only	PSR+ (Education or Policy or both)	p value[a] PSR+(Education or Policy or both) vs. PSR only
*TRO*s	Number of studies that analyzed significance on at least one outcome variable	11	8	**0.762**
	Number of outcome variables with significant positive impact, median (min-max)	1 (0-3)	1 (0-4)	
*CO*s	Number of studies that analyzed significance on at least one outcome variable	14	7	**0.357**
	Number of outcome variables with significant positive impact, median (min-max)	1 (0-3)	0 (0-2)	
Cost	Number of studies that analyzed significance on at least one outcome variable	12	4	**0.897**
	Number of outcome variables with significant positive impact, median (min-max)	1 (0-3)	1.5 (0-3)	
*MO*s	Number of studies that analyzed significance on at least one outcome variable	--	2	**NA**
	Number of outcome variables with significant positive impact	--	1	

CO: clinical outcome; MO: microbiological outcome; p: probability; max: maximum; min: minimum; NA: not applicable; PSR: patient-specific recommendation; TRO: treatment-related outcome; vs.: versus

[a]Comparison of the number of outcome variables with significant positive impact between the studies that analyzed the effect of PSR associated to Education or Policy or both strategies and those that analyzed only the effect of PSR. Comparison performed using *Mann-Whitney U* test

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3.2. Clinical and economic impact of clinical pharmacist interventions regarding antimicrobials on critically ill patients

3.2.1. Abstract

Background

A clinical pharmacist (CP) integrated in the Critical Care Area (CCA) team and performing interventions on antimicrobials may be cost-effective. Few comparative studies have evaluated this, and, to our knowledge, no studies regarding this issue have been carried out in CCAs in centres with a Program for Optimizing the use of Antibiotics (PROA).

Objective

To evaluate the impact of interventions on antimicrobials developed by a CP integrated in the CCA team, including the economic impact. To identify Drug Related Problems (DRPs) and medication errors detected by this CP.

Materials and methods

We conducted a retrospective evaluation of CP interventions (CPIs) on antimicrobials in adults admitted to an 18-bed CCA of a University Hospital with PROA over a 5–month period. CP routinely recorded information regarding: DRPs and medication errors, the drug involved, CPIs, clinical and economic impact of CPIs and acceptance of CPIs by physicians. Recorded costs included those associated with: change in antimicrobials, products for medication preparation, medication preparation and administration fees, adverse drug events, and CP time. Economic impact of CPIs was estimated as the difference in cost of 2 days of antimicrobial therapy after the CPI and the estimated cost in the case that the therapy prescribed before the CPI would have continued 2 days more. Several sensitivity analyses were performed.

Results

212 DRPs were detected, corresponding to 114 patients. Eighteen DRPs (8.5%) were medication errors. 96.2% of CPIs were considered important with improved patient care. None of the CPIs had any negative impact on patients. Physicians accepted 98% of the CPIs. We estimated a 10,905 € decrease in costs as a result of CPIs during the

study period (being the decrease 374 € and 127,772 € in the worst and best case scenarios, respectively). Therefore, 4.8 € were avoided per euro invested in CPs.

Conclusion: A CP performing interventions on antimicrobials integrated in the CCA team has a positive impact on patient care and decreases costs.

3.2.2. Introduction

A Clinical Pharmacist (CP) is a key member of a healthcare team who contributes significantly to optimization of pharmacotherapy and to medication errors prevention, among other aspects.[1] The Intensive Care Unit (ICU) is probably one of the hospital areas that best benefits from the incorporation of a CP to the healthcare team, due to the characteristics of the patients admitted to these units, with multiple comorbidities and complex pharmacotherapies. In addition, the prevalence of adverse drug reactions is documented as being much greater among patients admitted to the ICUs as compared to those in the general medical wards,[2] probably because these patients have more complicated treatments and are more closely monitored.

In acute care hospitals, up to 52% of the patients receive an antibiotic during their stay.[3] Several studies have shown that approximately 50% of antibiotic treatments may be unnecessary or inappropriate.[4] Pharmacists have a relevant role in optimizing patient antimicrobial treatment. Inappropriate use of antimicrobials may contribute to the increasing incidence of bacterial resistance in hospitalized patients, with the consequent impact on healthcare cost, among other effects. Resistance to antibacterials has become a serious global concern due to the increased consumption of anti-infective agents and the scarce development of new antibiotics. On the other hand, Baniasadi *et al.*[5] identified anti-infective agents as the class of drugs most frequently involved in Adverse Drug Events (ADEs), demonstrating the urgent need to establish measures to control the use of this group of drugs and prioritize CP interventions (CPIs) on antimicrobials, in order to rationalize their use.

Incorporating a CP in the ICU team and performing interventions on antimicrobials has significantly improved treatment-related outcomes (*e.g.* reduction in dosing errors[6]), clinical outcomes (*e.g.* reduction in length of stay in the ICU[6] and the rate of ADEs[6,7]) and economic results (*e.g.* reduction in drug expenditures[6,7] and ICU hospitalization costs[6,7]).

Nowadays, most of the hospitals have established a Program for Optimizing the use of Antibiotics (PROA) in their institutions. This consists of a multidisciplinary group that performs antimicrobial stewardship in the form of patient-specific interventions on antimicrobials, in which pharmacists are usually involved. CPIs on antimicrobials and interventions performed by the PROA are complementary because CPIs involve other aspects apart from the evaluation of the appropriateness of antimicrobial drug prescriptions concerning both the indication and the duration of the treatments. CPs also perform recommendations regarding dose optimization and change of the administration route, as well as detection of interactions, therapeutic duplications, medications errors, ADEs, *etc*. In our hospital, as many others, a PROA was established several years ago. The PROA in our institution evaluates the antimicrobial treatment only on selected patients that meet some predefined criteria (*e.g.* treatment with a combination of antimicrobials for more than 3 days, treatment with restricted-use antimicrobials for more than 3 days, or treatment with antimicrobial therapy for more than 7 days), while the CP evaluates the global treatment of all patients admitted to the Critical Care Area (CCA). In addition, while the PROA usually intervenes after the patient has received several doses of the antimicrobial treatment, the CP integrated *in situ* in the CCA team intervenes at the time physicians make prescriptions, most often when the drug has not yet reached the patient.

Most of the studies analyzing interventions on antimicrobials in hospitals with PROA evaluated the interventions made by the PROA multidisciplinary group as a whole, with pharmacists forming part of the group. Few comparative studies have analyzed the impact, including economic impact, of interventions on antimicrobials developed solely by the CP in adult patients admitted to the hospital setting. Most of these studies were developed in America and Asia, and only a few of them were conducted in Europe.[8-12] Furthermore, very few comparative studies have evaluated the clinical and the

economic impact of CPIs alone on antimicrobials in adult ICU patients,[6,7] and none of these were conducted in Europe. In addition, we have not found any comparative study analyzing the impact of CPIs on antimicrobials in an ICU and with PROA in the hospital, meaning that the CPIs were developed separately from the interventions performed by the PROA team, showing the additional benefits obtained from the CPIs in antimicrobial therapy besides those obtained from the participation of the pharmacist in PROA. From an economic endpoint, few studies have considered costs other than drug acquisition cost, such as costs corresponding to CP time spent performing the interventions, medication preparation and administration, and the economic impact of ADEs.

3.2.3. Objective

The main purpose of this study was to evaluate, in clinical practice, the added value of a CP performing interventions with the objective of optimizing antimicrobial treatments in the Critical Care Area, apart from the interventions developed by the PROA team (that includes CPs). This was performed by analyzing the impact of the CPIs, including the economic impact, and identifying Drug Related Problems (DRPs) and medication errors on antimicrobial drugs detected by this CP.

3.2.4. Materials and methods

Setting

This study was conducted in a University hospital in Spain. The hospital has 300 beds, 18 of them in the CCA (12 beds in the intensive care unit and 6 beds in the intermediate care unit). A CP is integrated into the CCA team. CP spends approximately 5 hours per day in the CCA and participates actively in daily rounds. CP reviews all active prescriptions every day and validates prescriptions of patients in the CCA at the same time as the physicians are prescribing the medication. CP mainly optimizes treatments and performs medication reconciliation and continuous monitoring of pharmacotherapy, evaluating the appropriateness of the treatment, administration

route and drug dosage, checking therapeutic duplications, interactions, effectiveness and toxicity of the treatments, *etc*. CP detects DRPs and medication errors and performs interventions intended to optimize patient pharmacotherapy.

At the end of the daily round, CP electronically records the information related to every detected DRP and medication error, and each CPI performed during that day is also recorded into the hospital information system. This routinely recorded information enables further evaluation of the effect of interventions developed by the CP in the CCA.

The same CP that is integrated into the CCA team forms part of the PROA of the hospital, which is formed by CPs, microbiologists and infectious disease physicians.

Study design and data selection

We conducted a retrospective observational study. We analyzed DRPs, medication errors and CPIs related to antimicrobials in inpatients admitted to the CCA in a 5-month period (from January 1, 2015 to May 31, 2015).

The current study aimed at evaluating the added value of interventions on antimicrobials performed by the CP integrated in the CCA team, apart from the interventions developed by the PROA team (that includes CPs), and apart from those performed by the central Pharmacy. Therefore, interventions performed by the PROA team and drug dose or dosing interval adjustments performed through the pharmacokinetics and pharmacodynamics area of the Pharmacy Service were not analyzed. CPIs related to antimicrobials for the treatment of certain diseases such as human immune deficiency virus, hepatitis or malaria were excluded from the analysis because antimicrobials used in those pathologies are chronic treatments that are not initiated during a critical care stay in response to an acute situation, and have a duration that goes beyond the length of hospital stay.

Based on Jiang *et al*. study,[7] which found a significant economic impact of pharmacist interventions on antimicrobials on the ICU with a sample size of approximately 90 patients per group, with and without intervention, we estimated that in 5 months we

would be able to collect 100 patients with CPIs so as to estimate the economic impact thereof.

Data collection

For this current study, data routinely recorded by the CP related to DRPs, medication errors and CPIs were extracted from the hospital information system.

Collected variables related to DRPs included: process in which DRPs were detected (daily review of prescriptions of every patient, validation of new prescriptions or prescriptions in which the physician makes any type of change, review of patient chart, *etc.*), DRP category (DRPs related to indication, safety or effectiveness), cause of the DRP, severity of the DRP (according to Schneider *et al.*´s methodology)[13], consequences of the DRP and the antimicrobial drug involved in the DRP. For DRPs considered to be medication errors, cause of the medication error, type of medication error and whether or not it reached the patient, were also collected. Collected variables related to CPIs included: CPI category, route used for transmitting the recommendation to physicians (orally, by documenting on the patient electronic chart or both), clinical impact and appropriateness of the CPIs, economic impact of the CPIs and the acceptance of the CPIs by physicians.

CPIs were classified into 6 mutually exclusive categories: change to a more cost-effective drug, change to a more effective drug, change to a more cost-effective administration route, drug discontinuation, initiating a new drug and modification of the dose or dosing interval of the same drug.

The clinical impact and appropriateness of the CPIs were assigned according to the Jiménez Torres methodology.[14] CPIs were classified as: i) inappropriate CPI for patient care; ii) CPI that led to reduction of costs without affecting treatment effectiveness; iii) important CPI that improves patient care; iv) very important CPI that prevents vital organ failure with a low probability of death, a serious ADE, or that increases the effectiveness of the treatment and prevents treatment failure; v) CPI that potentially prevents death.

In addition, some data regarding patients involved in the DRP were extracted from the hospital information system. These included: sex, age, Body Mass Index (BMI), department responsible for the patient, illness severity (evaluated using *Simplified Acute Physiology Score 3* (SAPS3) at CCA admission, comorbidities (cirrhosis, congestive heart failure, haematological cancer, metastasis, and immunocompromised state defined as Acquired Immune Deficiency Syndrome or having received chemotherapy, radiotherapy, immunosupressors or steroids over the last months), surgical interventions, isolation of multidrug-resistant bacteria during the CCA stay, length of hospital and CCA stay, duration of antimicrobial therapy and in-hospital mortality.

Economic impact analysis

The study intended to analyze the impact of CPIs in a real world scenario; therefore, randomization was not possible and finding two similar groups with and without CPI was not possible. Therefore, we had only one group with CPI, and the economic impact had to be estimated based on collected data. Methodology similar to that used by previous authors was followed.[15-19]

The economic impact of each CPI registered during the study period was estimated as the difference in the cost of the antimicrobial therapy recommended by the CP in his intervention and the estimated cost of the therapy without CPI. Cost with CPI referred to the cost of 2 days of antimicrobial treatment recommended by the CP in his intervention and accepted by the physician. Estimated cost without CPI referred to the cost of 2 days of antimicrobial treatment with the therapy before CP recommendations of changes. We assumed that the treatment change recommended by the CP would have happened 2 days later if the CP had not intervened.[9,11,20] Therefore, CPIs contribute to an earlier antimicrobial change (*e.g.* without CPI, the physician would have switched from an intravenous to an oral dosage form 2 days later than with the CPI).[19]

For estimating the difference in antimicrobial treatment costs with CPI versus without CPI for each CPI recorded during the study period, the cost of antimicrobial drugs and products for medication preparation (*e.g.* diluents, if required), and medication

preparation and administration fees were considered. This economic impact was also calculated by CPI category.

The cost of antimicrobial drugs and products for medication preparation was assigned considering selling laboratory price plus value-added tax in Spain as of June 8, 2016.[21] In the case of magistral formulas, the formula fee at our hospital was applied. Preparation fees at our hospital were used. Fees for sterile products are 1.16 € per preparation carried out in the horizontal laminar air flow cabin and 19.26 € per preparation carried out in the vertical air flow cabin, such as for ganciclovir preparation. A drug administration fee of 17.41 €[22] per drug administration was included for administration routes other than the oral route (*e.g.* intravenous, inhaled route).

For estimating the total economic impact of all CPIs performed during the study period, the economic impact of ADEs and the cost of CP time were added to the analysis. Therefore, the total cost difference with CPIs versus without CPIs was estimated as: the difference in antimicrobial treatment costs (antimicrobials + products for medication preparation + preparation fee + administration fee) with CPIs versus without CPIs + the impact of CPIs on ADE costs + the cost of CP time.

The impact of CPIs on ADE costs was estimated considering that CPIs in response to a DRP would either increase or decrease the likelihood of an ADE occurring (*e.g.* the likelihood of an ADE may increase if CP recommended an increase in the antimicrobial dose; the likelihood of an ADE may decrease if a drug was discontinued as a consequence of a CPI). Some CPIs intended to improve treatment effectiveness, yet they also increased the probability of ADEs, but with a favourable benefit/risk ratio. In those CPIs, the increased likelihood of ADEs occurring was considered.

The probability of an ADE occurring if the CPI had not been performed or the probability of an ADE occurring as a result of a CPI, in other words, the impact of the CPIs on the probability of ADEs, was fixed per CPI category. This figure was multiplied by the number of CPIs in that category and by the unit cost of an ADE.

As there is no validated and standardized method for imputing ADEs, the probability of ADEs was assigned to each CPI category by the main investigator according to Nesbit *et al*.´s methodology[15] and based on Gardner *et al*.[16] and Ibañez-García *et al*.[17] studies. In cases of discrepancy, the lowest probability of ADEs was attributed in order to be conservative. A decrease of 1% on the probability of ADEs occurring was assumed for CPIs involving change to a more cost-effective drug and change to a more effective drug (*e.g*. it was assumed that if an inadequate drug was used, probably higher drug doses or longer courses would be needed to achieve the therapeutic target, with a consequent increase in ADE probability. Therefore, the use of an adequate drug would decrease the probability of an ADE in comparison with the use of an inadequate drug). This figure was 10% for CPIs consisting in drug discontinuation and modification of the dose or dosing interval of the same drug due to overdosing. An increase of 10% in the probability of an ADE occurring was attributed to initiating a new drug and modification of the dose or dosing interval of the same drug due to underdosing. CPIs consisting in changing to a more cost-effective administration route were assumed not to change the probability of an ADE occurring.

The unit cost associated to an ADE was assigned according to the report developed by the European Comission[23] in 2016, which estimated the lowest and the highest cost estimates of an ADE based on published studies (minimum unit cost estimate of an ADE was set at 294 € and maximum unit cost estimate of an ADE at 5,689 €). In order to be conservative with the ADEs economic impact, the lowest value was used for the base-case scenario.

The cost of CP time included the cost of a CP performing interventions on antimicrobials in the CCA during the study period. Since 33% of the CPIs are related to antimicrobials, we assumed that 33% of CP time in the CCA was dedicated to those interventions; the CP is in the CCA for 5 out of his 7 working hours per day. Therefore, CP time cost was calculated as 0.33 x 5/7 x CP salary. Monthly CP salary for public hospital pharmacists in Navarra (Spain)[24] is 1,824 € plus 602 € for the enterprise cost, making a total of 2,426 €. Since the duration of the study was 5 months, CP salary during the study period was 12,130 €. This results in a CP cost of

0.33 x 5/7 x 12,130 €= 2,859 € for performing interventions on antimicrobials in the CCA during the study period.

All cost data were updated to the year 2016.

The ratio "avoided cost" to "invested money" (cost of CP time) was calculated as: [difference in antimicrobial treatment costs (antimicrobials + products for medication preparation + preparation fee + administration fee) with CPIs versus without CPIs + the impact of CPIs on ADE costs]/ cost of CP time.

When a CPI was not accepted by physicians, we assumed there was no impact on antimicrobial treatment costs or on ADE probability, since those CPIs were not implemented, but the invested money derived from CPI time was considered.

Due to uncertainty in economic impact estimation and the assumptions included in the calculations, several univariable sensitivity analyses were performed. The worst and best scenarios were also analyzed.

Statistical analysis was conducted using STATA 13.0®. Normality of variables was analyzed using the *Shapiro Wilk* normality test.

3.2.5. Results

A total of 212 DRPs were detected during the study period, which led to 212 CPIs, one for every DRP.

Patient characteristics and outcomes

One hundred and fourteen patients were involved in the 212 DRPs detected by the CP during the study period. Patient data are shown in Table 1.

Table 1. Data of the 114 patients involved in Drug Related Problems during the study period

Characteristic	Result
Sex (males), no. (%)	78 (68%)
Age (years), median (range)	69.5 (19-95)
BMI (kg/m^2), median (range)	25.8 (14.3-43.2)
Department responsible for the patient (surgical), no. (%)	50 (44%)
Illness severity:	
SAPS3 at CCA admission, median (range)	11.5 (0-65)[a]
Comorbidities:	
No comorbidity, no. (%)	48 (42%)
Cirrhosis, no. (%)	13 (11%)
Congestive Heart Failure, no. (%)	21 (18%)
Haematological cancer, no. (%)	4 (4%)
Metastasis, no. (%)	13 (11%)
Immunocompromised patients[b], no. (%)	36 (32%)
Patients who underwent surgery during hospital stay, no. (%)	70 (61%)
Patients with multidrug-resistant bacteria isolates during CCA stay, no. (%)	11 (9.6%)
Length of hospital stay (days), median (range)	15 (3-167)
Length of CCA stay (days), median (range)	4 (1-77)
Length of antimicrobial therapy (days), median (range)	10.5 (1-80)
In-hospital mortality, no. (%)	17 (15%)

BMI: Body Mass Index; CCA: Critical Care Area; no.: number; SAPS3: *Simplified Acute Physiology Score* 3

[a]74 available observations
[b]Defined as Acquired Immune Deficiency Syndrome or having received chemotherapy, radiotherapy, immunosupressants or steroids in last months.

A total of 58% of the patients had some comorbidity and 61% of the patients underwent surgery during their hospital stay. With regard to bacteria isolates, 12 multidrug-resistant bacteria were isolated in 11 patients, that are shown in Appendix 1.

Drug Related Problems (DRPs) and medication errors

DRPs were identified during validation of prescriptions (94%), daily review of every patient prescription (3%), review of patient chart (2%), review of patient pharmacotherapy (0.5%) and review of administrated medications (0.5%).

DRP categories and causes are shown in Table 2.

Table 2. Drug Related Problems (DRPs), their categories and causes

DRP category, no. (%)	DRPs, no. (%)	Cause of the DRP	
		Cause	**no. (%)**
Indication 97 (46%)	A drug is unnecessary 81 (84%)	Treatment duration is longer than appropriate	34 (42%)
		A more cost-effective administration route exists	30 (37%)
		A drug is not indicated	8 (10%)
		Therapeutic duplication problem exists	5 (6%)
		A more cost-effective drug exists	4 (5%)
	Need for additional treatment exists 16 (16%)	Treatment duration is shorter than appropriate	13 (81%)
		Need for combination therapy exists	2 (13%)
		An indication is not being covered	1 (6%)
Safety 92 (43%)	An overdosing problem exists 87 (95%)	Dose or dosing interval is inappropriate	87 (100%)
	Risk for adverse drug event exists 5 (5%)	An interaction exists	3 (60%)
		Allergy exists	1 (20%)
		A safer alternative exists	1 (20%)
Effectiveness 23 (11%)	An underdosing problem exists 21 (91%)	Dose or dosing interval is inappropriate	21 (100%)
	A drug is used inadequately 2 (9%)	Dosage form is inappropriate	1 (50%)
		Drug is not effective in the situation	1 (50%)

no.: number

Inappropriate dosing of the antimicrobials was the most frequently detected DRP (51%), followed by inappropriate duration of the therapy (22%) and having a more cost-effective administration route (14%).

According to the severity of the DRP, 207 DRPs (97.6%) would lead to making changes in the treatment or to increasing monitoring of the patient without producing changes in vital signs. Four DRPs (1.9%) would produce changes in the patient´s vital signs and would involve performing additional laboratory tests or invasive procedures on the patient if the CPI had not been performed. One DRP (0.5%) would not produce harm to the patient and would not require changes in the medical treatment.

A total of 177 DRPs (83.5%) would have consequences in terms of patient morbidity, one DRP (0.5%) would have consequences regarding efficiency, and 34 DRPs (16.0%)

would have consequences on both patient morbidity and efficiency, if the CP had not intervened.

Anti-infective agents involved in the reported DRPs are shown in Table 3.

Table 3. Anti-infective agents involved in the reported Drug Related Problems

Drug class	Drug related problems
	no. (%)
Beta-lactams	84 (40%)
Penicillins	50 (60%)
Cephalosporins	22 (26%)
Carbapenems	12 (14%)
Fluoroquinolones	40 (19%)
Triazoles	18 (8%)
Antivirals	17 (8%)
Glycopeptides	13 (6%)
Macrolides	11 (5%)
Sulfonamides	8 (4%)
Echinocandins	4 (2%)
Lincosamides	4 (2%)
Nitroimidazoles	4 (2%)
Others	9 (4%)

no.: number of Drug Related Problems during the study period.

Antibacterials were the antimicrobials most frequently involved in DRPs (82%), followed by antifungals (10%) and antivirals (8%). Three antibacterial classes accounted for more than half of the DRPs (23.6% penicillins, 18.9% fluoroquinolones and 10.4% cephalosporins).

Eighteen DRPs (8.5%) were considered medication errors, which affected 17 patients. Considering that during the study period 584 patients were admitted to the CCA, the medication error rate per patient was 0.03. Considering that during the study period there were 8,622 new medication prescriptions in general, the medication error rate per new medication prescription was 0.002. The mean number of drugs per prescription was 17.2.

All the medication errors were prescription errors and were due to: carelessness or forgetfulness (72.2%), lack of knowledge as judged by the CP (22.2%) and non-

compliance with guidelines or protocols (5.6%). Medication errors were associated with an erroneous antimicrobial dose in half of the cases, with an inadequate antimicrobial drug selection in 44% and with an inappropriate length of the antimicrobial therapy in 6% of the cases. The CP prevented most of these errors (65%) before they reached the patient. In all other cases, CP intervened after the error had reached the patient.

Clinical Pharmacist Interventions (CPIs)

CP performed one intervention in response to every DRP detected during the study period. CPIs consisted of modification of the drug dose or dosing interval of the same drug in 108 cases (51%). The rest included discontinuation of a drug in 47 cases (22%), change to a more cost-effective administration route in 30 cases (14%), initiating of a new drug in 16 cases (8%), change to a more cost-effective drug in 6 cases (3%) and change to a more effective drug in 5 cases (2%).

Four of the CPIs that involved a change to a more cost-effective drug, consisted on therapeutic de-escalation according to microbiological isolation. Three of them involved an antifungal (2 caspofungin and 1 voriconazole), and the other one involved an antibacterial agent (meropenem).

Most frequently, the CP verbally communicated the intervention to the physician, and documented the intervention on the electronic patient chart. However, in 32% of the cases, the CP did not document the intervention on the chart. Very rarely, in 1% of the cases, the CP registered the intervention on the patient record without first talking to the physician.

With regard to the clinical impact and appropriateness of the CPI, most CPIs (96.2%) were judged as important due to the improvement of patient care. Seven CPIs (3.3%) were classified as very important CPIs that prevented vital organ failure with a low probability of death, a serious ADE, or that increased the effectiveness of the treatment and prevented treatment failure. One CPI (0.5%) led to a reduction of costs without affecting treatment effectiveness. No CPIs had a negative impact on patient care quality. Almost all the documented CPIs were accepted by physicians (98%). Physicians did not accept five CPIs; 3 were recommendations for dose or dosing

interval modification due to overdosing and 2 were drug discontinuation recommendations.

Economic evaluation

With regard to the economic impact of CPIs on antimicrobial treatment costs (antimicrobials+ products for medication preparation+ preparation fee +administration fee), 156 CPIs (73.6%) led to a reduction of costs, 42 CPIs (19.8%) increased costs and the rest of the CPIs (6.6%) were neutral in terms of an economic aspect (5 of these CPIs were not accepted by the physician). The economic impact of CPIs is presented in Table 4. Table 5 shows the impact of CPIs on ADE probability and costs for each CPI category.

Table 4. Categories of Clinical Pharmacist Interventions (CPIs) and their economic impact on antimicrobial treatment costs

CPI Category	**CPIs, no. (%)**	**Difference in antimicrobial treatment costs (cost with CPIs -cost without CPIs)[a]**	
		All CPIs in each CPI category (€)	**Per CPI (€)[b]**
Modification of the dose or dosing interval of the same drug	108 (51%)	-3,531	-33
Drug discontinuation	47 (22%)	-4,088	-87
Change to a more cost-effective administration route	30 (14%)	-2,532	-84
Initiating a new drug	16 (8%)	+1,638	+102
Change to a more cost-effective drug	6 (3%)	-2,568	-428
Change to a more effective drug	5 (2%)	+56	+11
Total difference in antimicrobial treatment costs (cost with CPIs - cost without CPIs) during the study period: -11,025 €			

no: number of CPIs during the study period; €: euro.

[a]Difference in antimicrobial treatment costs (antimicrobials+ products for medication preparation+ preparation fee +administration fee) with CPIs versus without CPIs considering 2 days of antimicrobial treatment. A negative value denotes a decrease in cost due to CPI versus without CPI. A positive value denotes an increase in cost due to CPI versus without CPI.
[b]Calculated as the difference in antimicrobial treatment costs with CPIs versus without CPIs for all CPIs in that category divided by the number of CPIs in that category

Table 5. Impact of Clinical Pharmacist Interventions (CPIs) on Adverse Drug Event (ADE) probability and costs for each CPI category

CPI category	CPIs, no.[a]	Impact of CPIs on ADE probability for each CPI category[b]	Impact of CPIs on ADE costs for each CPI category (€)[c]	
			Minimum	Maximum
Modification of the dose or dosing interval of the same drug due to overdosing	84	-0.1	-2,470	-47,788
Drug discontinuation	45	-0.1	-1,323	-25,601
Change to a more cost-effective administration route	30	0	0	0
Modification of the dose or dosing interval of the same drug due to underdosing	21	+0.1	+617	+11,947
Initiating a new drug	16	+0.1	+470	+9,102
Change to a more cost-effective drug	6	-0.01	-18	-341
Change to a more effective drug	5	-0.01	-15	-284
Total estimated impact of CPIs on ADE costs (€)			-2,739	-52,965

no.: number of CPIs; €: euro.

[a]Only CPIs that were accepted by physicians were considered (no.= 207).
[b]A negative sign denotes a decrease in the probability of an ADE occurring as a result of the CPI. A positive sign denotes an increase in the probability of an ADE occurring as a consequence of the CPI.
[c]The estimated impact of CPIs on ADE costs was calculated by multiplying the number of interventions per each CPI category by the probability of an ADE occurring in that category of CPI and by the unit cost of an ADE (taken from the report of the European Comission[23], minimum unit cost estimate of an ADE 294 € and maximum unit cost estimate of an ADE 5,689 €). A negative value denotes a decrease in cost due to ADEs with the CPI vs. without CPI. A positive value denotes an increase in cost.

In more than half of the cases, CPIs would lead to a decrease in costs due to ADEs (68%); in 18% of the cases, CPIs would produce an increase in costs due to ADEs; and in the rest, CPIs would have no impact on costs due to ADEs (14%).

The CPI categories associated to the greatest decrease in costs due to ADEs per intervention were modification of the dose or dosing interval of the same drug due to overdosing, and drug discontinuation (minimum: -29 €; maximum: -569 €). The CPI categories associated to the greatest increase in costs due to ADEs per intervention were initiating a new drug, and modification of the dose or dosing interval of the same drug due to underdosing (minimum: +29 €; maximum: +569 €). The total estimated

impact of CPIs on ADE costs varied from a decrease of 2,739 € to a decrease of 52,965 € in the costs due to ADEs during the 5-month study period.

The total cost with CPIs during the 5-month study period was 10,905 € less than the estimated cost without CPIs in the base-case scenario. This included a reduction of 11,025 € in antimicrobial treatment costs (antimicrobials + products for medication preparation + preparation fee + administration fee) with CPIs due to an earlier change to the recommended antimicrobial therapy (assuming that the change to the treatment recommended by the CPI would have happened 2 days later if the CP had not intervened, the antimicrobial treatment cost of these 2 days was 13,406 € with CPIs versus 24,431 € without CPIs, making a difference of 11,025€) (table 4), the time spent by the CP performing interventions on antimicrobials in the CCA during the study period (an increase of 2,859 € with CPIs), and the estimated impact of CPIs on ADE costs (2,739 € less with CPIs). Therefore, 11,025 € + 2739 € - 2859 € = 10,905 € less with the CPIs. This resulted in avoiding a cost of 51 € per intervention and 96 € per patient with CPIs versus without CPIs. The ratio "avoided cost" to "invested money" or the return on investment was 4.8 €. Therefore, 4.8 € were avoided per 1 € invested in CPs.

Sensitivity analyses revealed that CPIs led to a decrease of 127,772 € in cost associated to antimicrobial treatments during the 5-month study period in the best-case scenario and to a decrease of 374 € in the worst-case scenario (table 6).

Table 6. Univariable sensitivity analyses of the economic impact of Clinical Pharmacist Interventions (CPIs) during the 5-month study period

Base-case scenario	Total cost difference with CPIs vs. without CPIs: -10,905 €			
Concept	**Base-case scenario (BCS)**	**Sensitivity analysis (SA)**	**Total cost difference with CPIs vs. without CPIs in SA scenario**[a]	**Reference**
Cost of products for medication preparation	Included	Not included	-10,725 €	In BCS, selling laboratory price plus value-added tax in Spain as of June 8, 2016[21] were used. In the case of magistral formulas, formula fee at our hospital was applied.
Cost of medication preparation	1.16 €/preparation in horizontal air flow cabin or 19.26 €/preparation in vertical air flow cabin	Not included	-10,736 €	In BCS, fees at our hospital were used.
Cost of medication administration	17.4 €/administration	Not included	-6,396 €	In BCS, public fee[22] was applied.
Unit cost estimate of an ADE	294 €	5,689 €	-61,131 €	Report of the European Comission.[23]
Unit cost estimate of an ADE	294 €	Halved (147 €)-doubled (588 €)	-9,535 €; -13,640 €	In SA, value was doubled and halved as in the paper by Nesbit *et al.*[15]
Impact of CPIs on ADE probability	See table 5	Halved - doubled	-9,535 €; -13,640 €	In SA, value was doubled and halved as in the paper by Nesbit *et al.*[15]
Impact of CPIs on ADE costs[a]	-2,739 € (see table 5)	Not included	-8,166 €	In BCS, the minimum unit cost per ADE was used.
Cost of CP time[a]	+2,859 €	Not included	-13,764 €	In BCS, public CP salary in Navarra (Spain) was used for calculations.[24]
Days when change to the treatment recommended by the CP would have happened without CPI	2 days	1-4 days	-5,559 €; -21,723 €	In SA, range from 1 to 4 days was obtained as mean difference in the length of antimicrobial courses with CPIs vs. without CPIs from Grill *et al.*[9] study (1 day) and Zhang *et al.* study[25] (4 days).
Economic impact of CPIs in the best-case scenario[b]: -127,772 €				
Economic impact of CPIs in the worst-case scenario[c]: -374 €				

ADE: Adverse Drug Event; CP: clinical pharmacist; vs.: versus; €: euro.

[a]A negative value denotes a decrease in cost due to CPIs vs. without CPIs. A positive value denotes an increase in cost.
[b]Calculated considering difference in antimicrobial treatment costs (antimicrobial drugs, products for medication preparation, medication preparation and administration fees) with CPIs versus without CPIs, the impact of CPIs on ADE costs, the maximum unit cost estimate of an ADE (5,689 €), doubling the probability of an ADE occurring and considering that change to the treatment recommended by the CP would have happened in 4 days without CPI. Cost of CP time was not considered.
[c]Calculated considering difference in cost of antimicrobial drugs with CPIs vs. without CPIs, and considering that change to the treatment recommended by the CP would have happened in 1 day without CPI and including cost of CP time. Difference in cost of products for medication preparation, medication preparation and administration fees with CPIs versus without CPIs and the impact of CPIs ADE costs were not considered.

3.2.6. Discussion

Our study shows that incorporating a CP in the CCA team and performing interventions on antimicrobial treatments had a positive impact on patient outcomes and also reduced costs.

Our study is the first, to our knowledge, to analyze the impact, including economic outcomes, of CPIs on antimicrobials apart from the interventions developed by the PROA team (that includes CPs) and carried out by a pharmacist integrated in the CCA team of a European hospital.

This study was developed in a hospital with a PROA. Our study showed that interventions on antimicrobials performed independently by the CP in parallel with the interventions developed by the PROA led to positive outcomes in clinical and economic terms. This justifies the added value of a CP developing interventions as a member of the CCA team in addition to the PROA of the hospital. Our study does not address the benefits of the CPIs, also existing, in areas other than antimicrobials.

Most of the DRPs were detected by the CP through prescription validation, demonstrating the relevance of a CP reviewing prescriptions to detect DRPs. In our study, most of the DRPs referred to inappropriate dosing of antimicrobials (51%), followed by inappropriate duration of the therapy (22%) and having a more cost-effective administration route (14%). Developing antimicrobial guidelines including recommendations regarding dose and duration of treatments, as well as implementing protocols for intravenous to oral switch, can contribute to reducing DRPs. In our hospital, these guidelines exist. In addition, information regarding drug dosing is available as a decision tool in the Computerized Physician Order Entry system during prescription validation and drug administration; however, there is still some room for improvement in this field and the participation of the CP in the CCA would always be necessary.

Almost all DRPs detected by the CP during the study period would be expected to have consequences on morbidity if the CP had not intervened (99.5%). In some studies evaluating CPIs on antimicrobials in different hospital wards, CPIs performed in

response to the detected DRPs led to better clinical outcomes, such as reduction of hospital and/or ICU stay,[6,26,27] mortality[26,27] and readmissions.[28]

The CP detected 18 medication errors on 17 patients during the study period. The medication error rate per patient admitted to the CCA during the study period was 0.03, and this rate per new medication prescription was 0.002. In the study developed by Khalili *et al.*,[1] CP detected 231 medication errors among the 956 patients admitted to a 60-bed infectious disease ward of a hospital during a 1-year study period, yielding medication error rates of 0.2 per patient and 0.04 per ordered medication. In the study by Tully *et al.*[29] carried out in a teaching hospital, pharmacists detected errors in 10.5% of the new medication orders. The reason for the difference in the rate of medication errors between our study and the others might be that, in contrast to those studies which analyzed interventions and errors involving all medication types, our study only included interventions and medication errors concerning antimicrobial treatments. CPIs on antimicrobials are 33% of all interventions developed by the CP in the CCA during the study period. In addition, comparison of medication errors rates between studies is difficult because the definition of the term medication error can change, and the type of setting and the time the CP spends performing interventions can also have some influence.

All detected medication errors were prescription errors. In most of the cases, a CP intervened before the error reached the patient. Therefore, incorporating a CP in the CCA team and reviewing prescriptions at the time and place where physicians make prescriptions can prevent medication errors and ADEs. Other studies also reached the same conclusion in different contexts. Kucukarslan *et al.*[30] evaluated the rate of preventable ADEs in patients admitted to general medicine units and receiving care from a healthcare team including a pharmacist with those receiving care from a team without a pharmacist. They found that the rate of preventable ADEs was reduced by 78% when a pharmacist was part of the healthcare team. Leape *et al.*[31] assessed the effect of pharmacist participation on medical rounds in the ICU on the rate of preventable ADEs. They observed a 66% decrease in the rate of preventable ADEs when a pharmacist participated on rounds as a full member of the ICU team.

In our study, half of the DRPs and medication errors were due to an inadequate antimicrobial dose, and half of the CPIs pretended to optimize the antimicrobial dose. In a study conducted in 2010, Khalili *et al.*[1] also found that most of medication errors were due to an incorrect dose. Ijo *et al.*[32] analyzed pharmacist interventions on antimicrobials in critically ill patients in USA and found that dose optimization was the most prevalent intervention type. Similar results were obtained by Dooley *et al.*[33] in a study conducted in 1998 in a hospital setting, not exclusive to ICU, and regarding interventions in all medication types. Therefore, a CP is a key professional in drug dosing adjustment partially due to his knowledge regarding drug pharmacokinetics and pharmacodynamics.

CPIs regarding antimicrobials had a relevant positive clinical impact on critically ill patient outcomes. We obtained data showing that nearly all the CPIs were considered important, with improvement of patient care (96%). In addition, the rate of acceptance of CPIs by physicians was high (98%) and it was consistent with results obtained by Leape *et al.*[31] This highlights the importance of interventions carried out by a CP.

From an economic point of view, interventions developed by a CP regarding antimicrobials on critically ill patients were advantageous. Our data showed that 4.8 € were avoided per 1 € invested in a CP. This finding coincides with the ratio reported in the study by Montazeri *et al.*[34] developed in the ICU, where a cost/benefit ratio of 1:4 was obtained. Results shown in different studies varied depending on the length of the study period, the ward type, the time that a CP spends performing interventions, variables included in the economic analysis, *etc*. This fact needs to be considered when comparing studies. In Zhou *et al.*´s study,[35] the ratio of the mean prophylactic antibiotic cost reduction to the mean incremental cost was 11.3:1. In Zhang *et al.*´s study,[25] the ratio of net mean cost savings in antibiotics to mean cost of pharmacist time was 18.79:1. In Ibañez-García *et al.*´s study,[17] the return on investment was 1.7 and in Wang et al´s study,[36] the ratio of the saving in antibiotic use to the cost of pharmacist time was 27.23:1.

Most of the published studies that analyzed the economic impact of CPIs on antimicrobials considered only the acquisition cost of the antimicrobials, without

including other concepts such as the cost of medication preparation and administration, the time CP spends performing interventions or the economic impact of ADEs.[8,9,11,37-39] Only a few authors included the economic impact of ADEs[15-17,19] or the cost of CP time[15,17,25,35,36] in their economic analysis. Our study considered other concepts apart from the cost of the antimicrobials, such as the cost of the products for medication preparation (*e.g.* diluents), medication preparation and administration fees, the economic impact of ADEs, and the cost of CP time. Including these issues in the analysis improves the estimation of the economic impact of the CPIs. In addition, performing sensitivity analyses, including ADE cost, is an appropriate approach, as ADE cost varies widely depending on the method used for its estimation.[40]

More than half of the CPIs provided financial benefits in the current study (74%). This was similar to that reported by Khalili *et al.*[1] (68%). Ijo *et al.*[32] reported that drug discontinuation, streamlining and intravenous to oral conversion were the type of interventions that provided most financial savings. In our study, drug discontinuation (4,088 €), modification of the dose or dosing interval of the same drug (3,531 €), and change to a more cost-effective drug (2,568 €) were the three CPI categories that provided higher avoided costs; and change to a more cost-effective drug was the CPI category which led to higher avoided cost per intervention (428 €). Prioritizing these types of interventions would result in greater cost savings.

The major limitation of this study is its retrospective and non-controlled design. However, it is difficult to have a control group in a CCA. Although it is a single centre study, many standardized data were used for cost estimates, facilitating extrapolation. In addition, several sensitivity analyses were conducted to analyze the impact of uncertainty on some variables. Time spent in the CCA by the CP must be considered when extrapolating results, 5 hours per day, 5 days a week in our study and performing one third of the interventions in response to antimicrobial DRPs.

Another limitation is that the pharmacist judged the severity of the DRPs, the clinical impact and appropriateness of the CPIs, and the probability of an ADE occurring, although predefined criteria based on literature were used[13-17] and several sensitivity analyses were performed.

In this study, the estimation of the impact of CPI was conservative. The impact of patient specific recommendations performed by the CP integrated in the CCA regarding anti-infective drugs were the only ones considered. Benefits arising from other activities performed by the CP, such as providing drug information and education to other healthcare professionals, performing data extraction and analysis on drug use or developing guidelines and protocols are difficult to quantify in economic terms and were not considered.

In addition, CPIs on antimicrobials accounted for 33% of all interventions developed by the CP in the CCA during the study period. Including all CPIs carried out in the CCA would probably lead to greater economic savings, as shown in other studies.[18,19,41]

3.2.7. Conclusions

Our results demonstrated that integrating a CP in the CCA team, developing interventions on antimicrobials, results in positive outcomes in terms of improving patient care and reducing healthcare costs, even in a hospital with a PROA. Further, multicentre, prospective and controlled studies are warranted.

3.2.8. References

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3.2.9. Supplementary data

Appendix 1. Multidrug-resistant bacteria isolates

Bacteria isolates	no. (%)
Enterobacter spp.	**3 (25.0%)**
AmpC cephalosporinase-producing *Enterobacter cloacae complex*	2
AmpC cephalosporinase-producing *Enterobacter aerogenes*	1
Pseudomonas aeruginosa	**3 (25.0%)**
Carbapenem-resistant *Pseudomonas aeruginosa*	2
Multidrug-resistant *Pseudomonas aeruginosa*	1
Other	
Methicillin-resistant *Staphylococcus aureus*	2 (16.7%)
AmpC cephalosporinase-producing and ertapenem resistant *Hafnia alvei*	1 (8.3%)
Enterococcus faecium Van A phenotype	1 (8.3%)
ESBL-producing *Escherichia coli*	1 (8.3%)
ESBL-producing *Klebsiella pneumoniae ssp pneumoniae*	1 (8.3%)

AmpC: Ampicillin class C; ESBL: extended-spectrum beta-lactamase; no.: number of bacteria isolates; *spp.*: species; Van: vancomycin; %: percentage of all bacterial isolates.

3.3 Effectiveness of inhaled antibiotic therapy in critically ill patients with respiratory infections

3.3.1. Abstract

Background

Inhaled antibiotics, in addition to systemic antimicrobials, may play a role in the treatment of severe respiratory infections in critically ill patients, providing high concentrations at the site of infection while minimizing systemic toxicity.

Purpose

To analyze the effectiveness of adding inhaled antibiotics to systemic antimicrobials in patients with respiratory infections admitted to the Critical Care Area (CCA). Secondly, to analyze their effect on renal function.

Materials and methods

We conducted a retrospective observational cohort study including adults admitted to the CCA during a 2-year period with respiratory infections treated with systemic antimicrobials in which sputum, bronchial aspirate, broncho-alveolar lavage and/or pleural fluid samples were obtained. Patients were divided into 2 groups: the treated group included patients with inhaled antibiotics in addition to systemic antimicrobials; and the control group with patients who did not receive inhaled antibiotics. Data were gathered from an electronic chart review.

Clinical improvement was the primary endpoint. Secondary outcomes were: resolution of fever, reduction of inflammatory parameters, length of hospital and CCA stay, length of systemic antimicrobial therapy, duration of intubation and mechanical ventilation, in-hospital mortality, hospital readmission, 30-day mortality, and reduction in creatinine clearance (CrCl).

A logistic regression model was performed in order to evaluate the effect of inhaled antibiotics in the primary endpoint adjusted by potential confounders.

Results

A total of 136 patients were included (93 in the control group, 43 in the treated group). The latter received 50 treatments with inhaled antibiotics (86% aminoglycosides, 14% colistimethate), 4 patients received more than one treatment. The median duration of inhaled therapy was 6 days (range: 1-112). The treated group had higher odds of clinical improvement after adjusting for confounders (adjusted odds ratio: 7.13; 95% confidence interval: 1.17-43.3; p=0.033). There were no significant differences in CrCl reduction between groups.

Conclusions

Adding inhaled antibiotics to systemic antimicrobials for the management of respiratory infections in critically ill patients has a positive impact on patients´ clinical improvement without increasing renal toxicity. Further studies are necessary to confirm this result.

3.3.2. Introduction

Respiratory infections have been recognized as an important clinical concern, with a significant impact on patients' morbidity and mortality. Ventilator-associated pneumonia (VAP) remains the leading cause of death related to nosocomial infection in critically ill patients.[1]

Given the limited penetration of some classes of antimicrobials into the lungs,[2] eradication of microorganisms and improvement of symptoms frequently require high doses and long courses of systemic antibiotics, which are frequently accompanied with drug-resistance and systemic toxicity, such as nephrotoxicity, ototoxicity and/or general toxicity.[3] Due to the problem of the increasing emergence of multidrug-resistant bacteria and the low rate of development of novel anti-infective agents, investigation of alternative delivery methods that improve bioavailability becomes essential.[4]

Various strategies exist to treat respiratory infections, and inhaled antibiotic therapy appears to be a successful one according to recent published studies. Inhaled antibiotics provide high concentrations at the site of infection while minimizing systemic exposure, and suppress biofilm formation.[5,6] This is especially relevant for antibiotics with a concentration-dependent mechanism of action such as aminoglycosides. In the study conducted by Abu-Salah *et al.*,[7] aerosolized antimicrobial agents achieved a 200–fold greater concentration in the respiratory secretions than levels achieved in the blood. It has been shown in multiple studies that antibiotic concentrations achieved in lung secretions as well as in broncho-alveolar lavage with targeted therapy far exceed the minimum inhibitory concentration of pathogens, with very low or non-detectable levels in the serum.[1] In addition, pulmonary delivery is non-invasive and avoids first-pass metabolism in the liver.[8]

The literature supporting the use of inhaled antibiotics, especially aminoglycosides, in patients diagnosed with cystic fibrosis and/or bronchiectasis is extensive, with satisfactory results.[3,9,10] It has been hypothesized that similar results obtained in patients with cystic fibrosis could be extrapolated to patients with other diagnoses.

Critically ill patients, particularly those with VAP, may benefit from adding inhaled antibacterial agents to systemic antimicrobial therapy. These patients, such as those diagnosed with cystic fibrosis, usually have an injured and inflamed airway epithelium due to the instrumentation of the airway, poor mucociliary clearance, and endotracheal tube biofilm.[1] However, the role of inhaled antibiotics in the treatment of acute infections, as in VAP and ventilator-associated tracheobronchitis (VAT), remains uncertain according to the limited evidence that support their use.[11-14] The type of devices, administration techniques, antibiotics, doses and indications are heterogeneous in published clinical papers,[15,16] making it difficult to draw firm conclusions. In addition, most of the studies are low quality and have a small sample size. Recent systematic reviews and meta-analyses have summarized early evidence supporting the use of inhaled antibiotics in patients diagnosed with VAP and VAT.[4,11,12,16] Inhaled antibiotics were associated with higher rates of clinical cure and resolution of signs and symptoms of VAP. However, a significant impact on mortality, microbiological eradication, duration of mechanical ventilation or length of Intensive

Care Unit (ICU) stay has not been demonstrated, except in the study by Valachis *et al*.[16] in which significant differences were found in microbiological eradication.

Most studies summarizing the utilization and effectiveness of inhaled antibiotics include only patients with mechanical ventilation.[5,15,17] Evidence in critically ill patients with respiratory infections other than VAP or VAT is scarce.[18]

On the other hand, multidrug-resistant pathogens are increasingly prevalent, compromising VAP treatment success and increasing mortality risk.[2] Recently, the emergence of the ESKAPE group of multidrug-resistant pathogens (*Enterococcus faecium, Staphylococcus aureus, Klebsiella pneumoniae, Acinetobacter baumanii, Pseudomonas aeruginosa and Enterobacter* spp.) has significantly challenged the treatment of patients in ICUs with VAP and other respiratory infections.[19] In critically ill patients with VAP or VAT due to multidrug-resistant Gram-negative bacteria, on which systemic therapy is failing and/or with systemic toxicity concerns, the option of nebulized antibiotics should be considered.[5] In addition, according to recent guidelines for hospital-acquired pneumonia and VAP published by the *Infectious Diseases Society of America* (IDSA) and the *American Thoracic Society* (ATS), inhaled antibacterial agents in combination with systemically administered antibiotics may be beneficial in patients with VAP due to Gram-negative bacilli that are only susceptible to aminoglycosides or polymyxins.[20]

In fact, ICU professionals in regions of the world with endemic multidrug-resistant or extensively drug resistant bacteria are responding to the lack of effective systemic antibiotics by adding inhaled antibiotics empirically to their VAP treatment regimens.[1] A global survey, carried out between 2014 and 2015 in 192 ICUs worldwide, indicated that nebulized antimicrobial agents are prescribed in mechanically ventilated patients in 70.3% of ICUs.[21] Given the morbidity and mortality associated with respiratory infections in these patients, the addition of inhaled antibiotics as adjunct therapy seems to be warranted in this scenario.

In the last few years advances in particle engineering have resulted in the development of different antibiotic formulations specifically designed for the inhaled route, such as dry powder and liposomal formulations. In Spain, aztreonam lysine,

colistimethate and tobramycin are the only antibacterial agents with marketed formulations specifically designed for the inhaled route. These formulations are only indicated to treat chronic lung infections due to *Pseudomonas aeruginosa* in patients diagnosed with cystic fibrosis. Indeed, aerosolized antibiotics have been used "*off-label*" for pneumonia in mechanically ventilated critically ill patients for around 40 years, but there is still no product approved for such treatment.[2] Several studies analyzing inhaled antibiotic therapy in respiratory infections and non-cystic fibrosis bronchiectasis have been performed with antibiotic formulations intended for intravenous use.[19,22,23]

With regard to safety issues, published studies on inhaled antibiotics have reported local adverse effects, mainly bronchospasm,[3,9,24,25] cough[10,24] and wheeze.[3,24] Systemic effects of inhaled antibiotics are rare due to their limited diffusion into systemic circulation. Renal toxicity being one of the most frequent adverse effects when administering these antibiotics by a systemic route, nephrotoxicity has been evaluated in some studies with inhaled antibiotics. However, studies analyzing nephrotoxicity found that inhaled antibiotics were not associated with an increased risk of renal toxicity.[9-11,16,19,25-29] Reports on nephrotoxicity related to inhaled antibiotics are mostly limited to single cases.[30-33]

Few studies have analyzed real world data of inhaled antibiotics in ICU patients without mechanical ventilation and diagnosed with acute respiratory infections different from VAP or VAT.[18] Furthermore, results in clinical practice may differ from those obtained from clinical trials.[34]

The main objective of this study was to evaluate the effectiveness of adding inhaled antibiotics to systemic antimicrobial treatment in critically ill patients, with or without mechanical ventilation, with respiratory infections. Secondly, we analyzed the effect of inhaled antibiotics on patients´ renal function.

3.3.3. Materials and methods

This retrospective, observational controlled cohort study was conducted in a University hospital in Spain. The hospital has 300 beds, 18 in the adult Critical Care Area (CCA) (12 beds in the ICU and 6 in the intermediate care unit). The study included all adult inpatients admitted to the CCA from January 1, 2014 to January 1, 2016 with respiratory infections treated at the CCA with systemic antimicrobial therapy in which sputum, bronchial aspirate, broncho-alveolar lavage and/or pleural fluid samples were obtained. We included patients that met inclusion criteria since 2014, previous patients were not included to avoid the influence of a change of prescribing policies with time.

Subjects were divided into 2 groups. The treated group included patients that received inhaled antibiotic therapy in addition and simultaneously to systemic antimicrobial treatment; and the control group which included patients that only received systemic antimicrobials without receiving inhaled antibiotics. Treatment with inhaled antibiotics was established according to physicians´ criteria.

Extemporaneous antibiotic solutions were given by the inhaled route to patients in the treated group. These preparations were performed with antibiotics indicated for systemic administration, with the exception of colistimethate that is also authorized for inhaled use. These solutions were prepared in syringes in the hospital Pharmacy Service in a horizontal air flow cabin using aseptic techniques.

Inhaled antibacterial agents were administered by a jet nebulizer (Micro-Cirrus®), that creates particles with a mass median aerodynamic diameter of 1.2 microns, in order to deposit the drug in the alveoli. The Micro-cirrus® nebulizer was selected in our hospital because it provided better results as compared with other jet nebulizer types in a pilot study (not published) with inhaled amphotericin B according to three criteria. Amphotericin B administered by Micro-cirrus® produced less reactive cough and less abnormal taste (indicating that the drug was mostly deposited in alveoli rather than in the tracheobronchial surface) and had less residual volume. This nebulizer allows the addition of a filter, to avoid bacteria or viruses from the gases inspired reaching the patient and to remove particles from exhaled gases. When a jet nebulizer was used for administering the inhaled treatment, oxygen flow was set at 8 L/min and an additional

40 to 50% of antibiotic solution was prepared due to losses produced during the inhalation and to the residual volume of the nebulizer. When the patient was under mechanical ventilator during the treatment with inhaled antibiotics, the drug was nebulized through the ultrasonic nebulizer of the Servo-I® ventilator. It was considered that there was no residual volume in the ultrasonic nebulizer.

For the current study, variables were extracted from patient electronic charts. These included patients´ characteristics: age, sex, Body Mass Index (BMI), comorbidities, type of stay in the CCA (ICU, intermediate care unit, or both), reason for admission to the CCA, surgery during hospital stay, infectious disease diagnosis, fever and inflammatory parameters (white blood cell count, C-reactive protein, procalcitonine) at the beginning of the treatment with systemic antibiotics, worst *Sequential Organ Failure Assessment* (SOFA) value during hospital stay, requirement of mechanical ventilation and/or intubation during hospital stay, mechanical ventilation and/or intubation previous to the beginning of systemic antimicrobials, and mechanical ventilation and/or intubation previous to the beginning of inhaled antibiotics. Collected comorbidities included immunosuppression, Diabetes Mellitus, chronic obstructive pulmonary disease, obstructive sleep apnea syndrome, oncologic diagnosis, metastasis, congestive heart failure, chronic kidney disease and cirrhosis.

With regard to systemic antimicrobial therapy, the following variables were collected: treatment indication (targeted treatment/empiric treatment) and duration of systemic antimicrobial therapy. As regards inhaled antibiotic treatment of patients in the treated group, treatment indication (following the same classification as for systemic therapy), inhaled antibiotic and its duration were collected. Results of sputum, bronchial aspirate, broncho-alveolar lavage and/or pleural fluid samples obtained during the antimicrobial treatment (both inhaled and systemic) were analyzed in order to identify bacteria isolates and their antibiogram.

Clinical improvement was established as the primary endpoint to determine the effectiveness of inhaled antibiotics. Clinical improvement was assumed if physicians described an improvement of the patient´s general and clinical situation in the patient

clinical record at the end of the systemic antimicrobial therapy in comparison with at the beginning.

In addition to the above, other variables were collected, which were considered secondary endpoints: resolution of fever, reduction in inflammatory parameters (white blood cell count, C-Reactive Protein and procalcitonine), length of hospital stay, length of stay in the CCA, length of ICU stay, length of systemic antimicrobial therapy, duration of intubation, duration of mechanical ventilation, and in-hospital mortality (all-cause mortality), hospital-readmission within the following 30 days and 30-day mortality (mortality within the 30 days after hospital discharge). Resolution of fever was considered positive in patients with more than 38ºC at the beginning of systemic antimicrobial treatment and less than 38ºC at the end of that treatment. Reduction in inflammatory parameters was considered positive in patients with lower absolute values at the end of systemic antimicrobial treatment in comparison with values at the beginning of systemic antibiotic therapy.

To analyze the effect of inhaled antibiotics on patients' renal function, serum creatinine value at the beginning and at the end of systemic antimicrobial treatment was obtained. Creatinine clearance (CrCl) at the beginning and at the end of systemic therapy was calculated using the *Cockroft-Gault* equation.[35] When serum creatinine was lower than 0.6 mg/dl, a value of 0.6 mg/dl was assumed for CrCl calculation. The percentage of patients that had a reduction in CrCl at the end of the systemic therapy compared with at the beginning, and the percentage of reduction of CrCl were compared between groups.

Data were analyzed using STATA® 13.0. Normality of variables was analyzed using the *Shapiro-Wilk* normality test. Continuous variables were compared between groups with *Student´s t* test or *Mann- Whitney U* test and dichotomous data by *Chi-square.* A logistic regression model was performed to estimate the effect of inhaled antibiotics on the primary endpoint adjusted by confounding factors. Adjusted odds ratio was used to quantify the association.

3.3.4. Results

A total of 136 patients were included in the study, 43 in the treated group and 93 in the control group. Patients´ characteristics are shown in Table 1.

Table 1. Patients' characteristics

Characteristic	**Control group (n=93)**		**Treated group (n=43)**		**p-Value**
	No. Obs.	**Results**	**No. Obs.**	**Results**	
***Age* (years),** mean (SD)	93	69.1 (13.4)	43	67.6 (9.3)	0.254[a]
***Sex* (males),** no. (%)	93	60 (64.5%)	43	28 (65.1%)	0.946[b]
***BMI*,** mean (SD)	93	24.3 (4.1)	43	24.5 (4.4)	0.590 [a]
Comorbidities (YES), no. (%)					
None	93	8 (8.6%)	43	2 (4.7%)	0.412[b]
Immunosupression	93	47 (50.5%)	43	24 (55.8%)	0.567[b]
Diabetes Mellitus	93	26 (28.0%)	43	10 (23.3%)	0.563[b]
Chronic obstructive pulmonary disease	93	15 (16.1%)	43	9 (20.9%)	0.495[b]
Obstructive sleep apnea syndrome	93	7 (7.5%)	43	0 (0%)	0.065[b]
Oncologic diagnosis	93	40 (43.0%)	43	20 (46.5%)	0.702[b]
Metastasis	93	18 (19.4%)	43	11 (25.6%)	0.410[b]
Congestive heart failure	93	29 (31.2%)	43	7 (16.3%)	0.067[b]
Chronic kidney disease	93	21 (22.6%)	43	12 (27.9%)	0.500[b]
Cirrhosis	93	8 (8.6%)	43	9 (20.9%)	**0.043**[b]
Number of comorbidities, mean (SD)	93	2.3 (1.3)	43	2.4 (1.3)	0.620[a]
Type of stay in CCA, no. (%)	93	--	43	--	0.560[b]
ICU	93	53 (57%)	43	26 (60.5%)	0.702[b]
Intermediate care unit	93	15 (16.1%)	43	4 (9.3%)	0.286[b]
ICU+intermediate care unit	93	25 (26.9%)	43	13 (30.2%)	0.686[b]
Reason for CCA admission, no. (%)	93	--	43	--	0.061[b]
Acute respiratory distress syndrome	93	43 (46.2%)	43	10 (23.3%)	**0.011**[b]
Postoperative management	93	11 (11.8%)	43	13 (30.2%)	**0.009**[b]
Sepsis or septic shock	93	16 (17.2%)	43	7 (16.3%)	0.894[b]
Bleeding	93	7 (7.5%)	43	5 (11.6%)	0.433[b]
Respiratory infection	93	3 (3.2%)	43	1 (2.3%)	0.773[b]
Cardiopulmonary arrest	93	1 (1.0%)	43	2 (4.7%)	0.187[b]
Other	93	12 (12.9%)	43	5 (11.6%)	0.834[b]
Surgery during hospital stay, no. (%)	93	24 (25.8%)	43	18 (41.9%)	0.060[b]
***Infectious disease diagnosis*,** no. (%)	93	--	43	--	0.538[b]
Sepsis or septic shock due to pneumonia or tracheobronquitis	93	16 (17.2%)	43	10 (23.3%)	0.404[b]
Pneumonia without sepsis	93	41 (44.1%)	43	15 (34.9%)	0.311[b]
Tracheobronchitis without sepsis	93	36 (38.7%)	43	18 (41.9%)	0.727[b]
BASAL fever (YES), no. (%)	93	24 (25.8%)	43	12 (27.9%)	0.796[b]
BASAL inflammatory lab data, median (range)					
White blood cell count (10 E9/L)	91	11.4 (0.7-52.9)	41	8.8 (0.4-25.3)	0.204[c]

Table 1 (continued)

Characteristic	Control group (n=93)		Treated group (n=43)		p-Value
	No. Obs.	Results	No. Obs.	Results	
BASAL inflammatory lab data, median (range)					
C-Reactive protein (mg/L)	89	9.5 (0.1-44.8)	36	10.9 (0.1-33.8)	0.889[c]
Procalcitonine (ng/mL)	69	0.4 (0.1-175.2)	27	2.1 (0.0-83.4)	**0.015**[c]
Worst SOFA during hospital stay, median (range)	88	6 (0-20)	42	10 (1-20)	**<0.001**[c]
Mechanical ventilation (MV) or intubation (INTB), no. (%)					
MV during hospital stay	93	71 (76.3%)	43	35 (81.4%)	0.509[b]
INTB during hospital stay	93	23 (24.7%)	43	24 (55.8%)	**<0.001**[b]
MV prior to systemic antibiotics	93	10 (10.8%)	43	14 (32.6%)	**0.002**[b]
MV prior to inhaled antibiotics	--	--	43	28 (65.1%)	NA
INTB prior to systemic antibiotics	93	2 (2.2%)	43	9 (20.9%)	**<0.001**[b]
INTB prior to inhaled antibiotics	--	--	43	16 (37.2%)	NA

BASAL: at the beginning of systemic antimicrobial therapy; BMI: Body Mass Index; CCA: Critical Care Area; ICU: Intensive Care Unit; NA: not applicable; No. Obs.: number of observations that had the indicated characteristic; p: probability in the comparison test; SD: standard deviation; SOFA: *Sequential Organ Failure Assessment* value.

a: *Student´s t* test
b: *Chi-square*
c: *Mann- Whitney U* test

Patients in the treated group presented significantly higher procalcitonine values at the beginning of systemic antimicrobial therapy and worse SOFA values during hospital stay than patients in the control group. Cirrhosis, intubation during hospital stay, and mechanical ventilation and intubation prior to systemic therapy were more frequent in patients with inhaled antibiotics. Acute respiratory distress syndrome and postoperative management as reasons for admission to the CCA were also different between groups.

With regard to infectious disease diagnosis, 55 patients had hospital-acquired pneumonia or tracheobronchitis (31 in control group and 24 in the treated group, p=0.007). Thirteen of them were related to mechanical ventilation (4 in control group and 9 in treated group, p=0.002).

Systemic antimicrobial therapy was mainly initiated empirically (not as targeted therapy), in 96.8% of patients from the control group and in 83.7% from the treated group. Inhaled antibiotics were placed as targeted treatments (not empirical therapies) in 72.1% of the cases.

Four patients in the treated group received different non-simultaneous inhaled antibacterials, making a total of 50 treatments with inhaled antibacterial agents in 43 patients. Half of the inhaled treatments were tobramycin, 20% gentamycin, 16% amikacin and 14% colistimethate. The prescribed dose for tobramycin was 100-150 mg every 12 hours, for gentamycin 100-200 mg every 12 hours, for amikacin 250-500 mg every 12 hours and for colistimethate 1 million international units every 8 hours (for a patient to receive these doses of these drugs an additional 40 to 50% of antibiotic solution was prepared for jet nebulizer administrations).

The majority of inhaled treatments were administered by a jet nebulizer, except for seven treatments that were administered through an ultrasonic nebulizer. In general, a bronchodilator was administered prior to the administration of the inhaled antibacterial, except for 3 cases in which a bronchodilator was not prescribed simultaneously to the inhaled antibiotic treatment. The median duration of the inhaled antibiotic therapy was 6 days, ranging from 1 to 112 days. Bacteria isolates in the sputum, bronchial aspirate, broncho-alveolar lavage and/or pleural fluid samples obtained during the antimicrobial treatment in patients of the treated group are presented in Table 2. These correspond to 47 bacteria isolates identified in 31 patients with target inhaled therapy. No bacteria isolate was identified in patients with empiric inhaled therapy. Thirteen of the 47 bacteria (27.7%), isolated in 12 patients were multidrug-resistant bacteria.

Table 2. Bacterial isolates in patients in the treated group

Bacteria isolates	no. (%)
Pseudomonas aeruginosa	**13 (27.7%)**
Multidrug-resistant *Pseudomonas aeruginosa*	2
Carbapenem-resistant *Pseudomonas aeruginosa*	1
Other *Pseudomonas aeruginosa*	10
Enterobacter spp.	**5 (10.6%)**
AmpC cephalosporinase-producing *Enterobacter cloacae complex*	4
AmpC cephalosporinase-producing *Enterobacter aerogenes*	1
Acinetobacter spp.	**4 (8.5%)**
Acinetobacter junii	2
Acinetobacter baumanii	1
Carbapenemase producing multi-resistant *Acinetobacter baumannii*	1
Klebsiella spp.	**4 (8.5%)**
Klebsiella pneumoniae ssp pneumoniae	2
ESBL-producing *Klebsiella pneumoniae ssp pneumoniae*	1
Klebsiella oxytoca	1
Staphylococcus aureus	**4 (8.5%)**
Inducible MLSb phenotype *Staphylococcus aureus*	2
Other *Staphylococcus aureus*	2
Citrobacter spp.	**3 (6.4%)**
Citrobacter freundii	2
AmpC cephalosporinase-producing *Citrobacter youngae*	1
Other	
Escherichia coli	3 (6.4%)
Serratia marcescens	3 (6.4%)
Stenotrophomonas maltophilia	3 (6.4%)
Enterococcus faecalis	2 (4.3%)
Streptococcus pneumoniae	2 (4.3%)
Haemophilus influenzae	1 (2.1%)

AmpC: ampicillin class C; ESBL: extended-spectrum beta-lactamase; MLSb: macrolide, lincosamide and streptogramin B; no: number of bacteria isolates; *spp.*: species; %: percentage of all bacterial isolates.

Among patients in the control group, a total of 65 bacteria isolates were identified in the sputum, bronchial aspirate, broncho-alveolar lavage and/or pleural fluid samples obtained during the antimicrobial treatment in 45 patients. Bacteria isolates in patients in the control group are presented in Table 3. Seven of the 65 bacteria (10.8%), isolated in 6 patients were multidrug-resistant bacteria.

Table 3. Bacterial isolates in patients in the control group

Bacteria isolates	no. (%)
Staphylococcus spp.	**15 (23.1%)**
Staphylococcus aureus	9
Methicillin-resistant *Staphylococcus aureus*	5
Staphylococcus epidermidis	1
Streptococcus spp.	**12 (18.5%)**
Alpha-haemolytic	
Streptococcus pneumoniae	9
Streptococcus constellatus	1
Beta-haemolytic	
*Streptococcus agalactiae (*Group B)	1
Group C streptococci	1
Stenotrophomonas maltophilia	**7 (10.8%)**
Enterobacter spp.	**6 (9.2%)**
Enterobacter cloacae complex	5
Enterobacter aerogenes	1
Escherichia coli	**6 (9.2%)**
Klebsiella spp.	**5 (7.7%)**
Klebsiella oxytoca	4
Klebsiella pneumoniae	1
Citrobacter spp.	**3 (6.4%)**
Citrobacter freundii	2
Amp C cephalosporinase-producing *Citrobacter youngae*	1
Enterococcus spp.	**3 (4.6%)**
Enterococcus faecalis	2
Enterococcus faecium	1
Pseudomonas aeruginosa spp.	**3 (4.6%)**
Multidrug-resistant *Pseudomonas aeruginosa*	1
Other *Pseudomonas aeruginosa*	2
Other	
Achromobacter xylosoxidans	1 (1.5%)
Ochrobactrum anthropi	1 (1.5%)
Acinetobacter baumannii	1 (1.5%)
Citrobacter freundii	1 (1.5%)
Hafnia alvei	1 (1.5%)
Haemophilus influenzae	1 (1.5%)
Moraxella catarrhalis	1 (1.5%)
Serratia marcescens	1 (1.5%)

AmpC: ampicillin class C; no: number of bacteria isolates; *spp.*: species; %: percentage of all bacterial isolates.

Significant differences were obtained in the percentage of patients with multidrug-resistant bacteria between both groups (27.9% in the treated group vs. 6.5% in the control group, p=0.001).

Outcome variables are shown in Table 4.

Table 4. Outcome variables

Outcome variable	Control group (n=93)		Treated group (n=43)		p-Value
	No. Obs.	Result	No. Obs.	Result	
Primary endpoint					
Clinical improvement, no. (%)	93	65 (69.9%)	43	31 (72.1%)	0.793[a]
Secondary endpoints					
Resolution of fever, no. (%)	24	22 (91.7%)	12	12 (100.0%)	0.303[a]
Reduction in inflammatory lab data, no. (%)					
In white blood cell count	71	43 (60.6%)	25	11 (44%)	0.151[a]
In C-Reactive protein	63	49 (77.8%)	15	12 (80%)	0.851[a]
In procalcitonine	22	12 (54.6%)	8	7 (87.5%)	0.098[a]
Length of stay (days), median (range)					
Hospital stay	93	19 (2-167)	43	23 (3-160)	0.064[b]
CCA stay	93	7 (1-46)	43	12 (2-70)	**0.011**[b]
ICU stay	78	5 (1-46)	39	10 (2-48)	**0.003**[b]
Length of therapy, median (range)					
Days with systemic antimicrobials	93	13 (2-52)	43	17 (2-133)	**0.032**[b]
Hours with INTB	21	49 (3-265)	22	77 (8-355)	0.489[b]
Hours with VM, including INTB	51	59 (2-552)	31	75 (1-570)	0.450[b]
In-hospital mortality, no. (%)	93	23 (24.7%)	43	12 (27.9%)	0.694[a]
Hospital-readmission within 30 days, no. (%)	93	11 (11.8%)	43	6 (14.0%)	0.727[a]
30-day mortality[c], no. (%)	69	8 (11.6%)	30	1 (3.3%)	0.189[a]
Patients with reduction in Crcl, no. (%)	80	25 (31.3%)	26	4 (15.4%)	0.115[a]
Reduction in CrCl (%), median (range)	25	25% (5-67)	4	14% (11-48)	0.255[b]

CCA: Critical Care Area; CrCl: Creatinine clearance; ICU: Intensive Care Unit; INTB: intubation; MV: mechanical ventilation; No.Obs: number of observations that had the indicated variable; p: probability of the comparison test.

a: *Chi-square*
b: *Mann- Whitney U* test
c: mortality within the 30 days after hospital discharge

Clinical improvement was controlled for potential confounders (age, sex, BMI, comorbidities, ICU stay, acute respiratory distress syndrome as a reason for admission to the CCA, surgery during hospital stay, sepsis or septic shock and pneumonia without sepsis as infectious disease diagnosis, fever and inflammatory parameters at the beginning of the systemic antimicrobial therapy, worst SOFA value during hospital stay, and mechanical ventilation and intubation previous to the beginning of systemic antimicrobial therapy). Confounding factors finally included in the model were: age, sex, BMI, comorbidities, ICU stay, surgery during hospital stay, sepsis as the infectious disease diagnosis, inflammatory parameters at the beginning of the systemic

antimicrobial therapy (white blood cell count, C-Reactive protein and procalcitonine), worst SOFA value during hospital stay and mechanical ventilation previous to the beginning of systemic antimicrobial therapy. After controlling for potential confounders, the treated group was independently associated with clinical improvement (adjusted odds ratio: 7.13; 95% confidence interval: 1.17,43.3; p=0.033).

There were no significant differences in the number of patients that had a reduction in CrCl between both groups (p=0.115), nor in the percentage of reduction (p=0.255). With regard to patients that had a reduction in CrCl at the end of the systemic therapy having CrCl> 30 ml/min at the beginning, 4 patients in the control group and 1 patient in the active group had CrCl<30 ml/min at the end of the systemic therapy (p=0.602). As regards safety, no adverse effects were directly attributable to inhaled antibiotics during the studied period, and no inhaled antibiotic had to be discontinued due to safety issues.

3.3.5. Discussion

We analyzed the effect of adding different inhaled antibiotics to systemic antimicrobial therapy in critically ill patients, with and without mechanical ventilation, diagnosed with different respiratory infections. After controlling for confounding factors, the addition of inhaled antibiotic was associated with higher odds of achieving clinical improvement.

Our study is the first one, to our knowledge, to include both critically ill patients with and without mechanical ventilation and patients with different infectious respiratory diseases, both nosocomial and community-acquired. In contrast to most papers regarding the efficacy or safety of inhaled antibiotics that are restricted to patients with cystic fibrosis[10] and ventilator-associated infections (VAT and VAP)[11,12,16], and/or include patients with only one diagnosis per study, this being VAT, VAP, non-cystic fibrosis bronchiectasis,[25] cystic fibrosis,[36] *etc*. In our study, subgroup analysis by type of infection was not possible due to the limited number of patients included.

Most of the patients in our study received inhaled aminoglycosides (86%), and some colistimethate (14%); *Pseudomonas aeruginosa* was the most frequently isolated bacteria (28%). These antibiotics correspond to the inhaled agents included in the majority of the studies,[19,37] and are the first choice inhaled antibiotics for the treatment of bronchial infections caused by *Pseudomonas aeruginosa*.[38] Although in Solé-Lleonart *et al*.[21] and Ehrmann *et al.*[37] surveys, colistin was the most frequently administered inhaled antibiotic followed by tobramycin. However, studies comparing tobramycin and colistin in patients with cystic fibrosis, suggest that tobramycin is more effective.[36,39]

In our study, inhaled antibiotic treatments were mostly administered by jet nebulizer (86%), as in the Karvouniaris *et al.* study,[40] and the Quon *et al*.[23], Sole-Lleonart *et al.*[15] and Ehrmann *et al*.[37] reports. However, both the optimal nebulizer type and technique remain indeterminate to date.[23]

As most of our patients received inhaled antibiotics for an acute infection or an acute process of a chronic situation, the median duration of inhaled antibiotic therapy was 6 days, shorter than that described in published studies that include other chronic diagnoses that lead to longer antibiotic durations, for example up to 2 years.[41] Therefore, our conclusions may not apply to other chronic diagnoses such as cystic fibrosis.

According to our data, adding inhaled antibiotics to systemic antimicrobial therapy has a significant impact on patients´ clinical improvement. Other studies also reached the same conclusion in patients diagnosed with VAP and VAT, showing that patients treated with inhaled antibiotics had higher rates of clinical cure and resolution of signs and symptoms. Furthermore, these studies did not find a statistically significant impact on mortality, toxicity, microbiological cure, duration of mechanical ventilation or ICU length of stay.[1,4,11,12] However, in the meta-analysis conducted by Valachis *et al*.[16] a significant improvement in clinical response, microbiological eradication and infection-related mortality was obtained with the addition of aerosolized colistin to the treatment with the same antibiotic administered by intravenous route in patients diagnosed with VAP. Although, no significant differences were found in overall mortality or nephrotoxicity.

Studies analyzing the effect of inhaled antibiotics in patients diagnosed with non-cystic fibrosis bronchiectasis showed that inhaled antibiotics produced a significantly greater reduction in bacterial loads and were associated with higher odds of achieving complete bacterial eradication without a higher emergence of bacterial resistance. Moreover, inhaled antibiotics significantly reduced the risk of acute exacerbations.[3,13] In our study, bacterial eradication and reduction in bacterial loads were not studied because isolates are rarely collected after clinical resolution of cases in clinical practice. The scarce data available concerning the impact of inhaled antibiotics in the emergence of antimicrobial resistance suggests that their use is not associated with the development of new antibiotic resistance.[1,29] However, future investigation is needed to determine the effect of inhaled antibiotics on multidrug-resistant organisms.

Other outcome variables apart from clinical improvement were also collected in our cohort of patients. The outcome variable most directly related to antibiotic treatment was selected as the main outcome variable. However, due to the observational nature of the study and the difference in patients´ characteristics between both groups, adjusting by confounders was necessary. In fact, without adjusting, no statistical significant difference was found in the clinical improvement between groups. However, treated group included more severe or complicated cases. Patients with inhaled therapy had worse SOFA values, higher frequency of cirrhosis, more admissions to CCA for postoperative management, worse procalcitonine values at the beginning of systemic antimicrobial therapy and a higher use of intubation during hospital stay, and mechanical ventilation and intubation prior to systemic therapy.

Therefore, due to the observational, retrospective and controlled nature of the present study, our results must be taken with caution and the study must be considered as a pilot study. Furthermore, the project was carried out on a single site and included a small simple size. However, it includes different infectious respiratory diseases representing real-world scenarios.

Another limitation of our study is that the effect of variables not recorded in electronic patient charts could not be analyzed. In addition, even if clinical improvement is frequently used as an outcome variable, its definition is not standardized. In future

studies, objective and uniform scales including health-related quality of life scores, such as the Clinical Pulmonary Infection Score[29] or the St. George Respiratory Questionnaire scale scores[25] have to be implemented. Although some physicians in our study are more prone to using inhaled therapy than others and physicians evaluating patients' clinical improvement were blinded to the study thus decreasing the risk of bias.

Comparison between studies is difficult due to the variability in inhaled antibiotics use and in study methods. For example, differences exist in study designs (single arm or versus placebo, with or without concomitant systemic antimicrobials, *etc*.), type of patients (hospitalized patients, outpatients, critically ill patients, *etc*.), antimicrobials and doses, formulations, duration of therapies, nebulizer type, administration techniques, causative microorganisms, *etc*. This variability can also interfere with the extrapolation of results. Although, in our hospital inhaled antimicrobials are used similarly to other centres. Thus, there is a need for standardizing practices and for developing guidelines regarding the use of inhaled antibiotics.

3.3.6. Conclusions

Inhaled antibiotics, administered simultaneously to systemic antimicrobials to treat a wide range of respiratory infections in critically ill patients, have a positive impact on patients´ clinical improvement and they are not associated with increased renal toxicity. Further studies are warranted to confirm these results. Standardization of inhaled antibiotic treatments is necessary for conducting larger multicentre randomized trials and observational studies.

3.3.7. References

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4. DISCUSIÓN

La evidencia disponible hasta le fecha, así como los resultados del estudio observacional que hemos realizado en nuestro centro, ponen de manifiesto el impacto positivo de las intervenciones farmacéuticas sobre antimicrobianos en pacientes adultos ingresados en términos de optimización de parámetros relacionados con el tratamiento y/o la prescripción (selección y uso racional de antimicrobianos, duración de la terapia, vía de administración, pauta posológica, *etc*.) y mejoría clínica de los pacientes, así como reducción del gasto vinculado a la asistencia sanitaria.

Sin embargo, la calidad de la evidencia es en general pobre, ya que en la mayoría de los casos no se realiza aleatorización, no se mantiene ciego en el estudio, *etc*.[1] Por ello, sería conveniente completar estos estudios con otros con metodología más adecuada para poder obtener resultados más objetivos acerca del impacto de las intervenciones farmacéuticas.

Son pocos los estudios que analizan el impacto del farmacéutico clínico en áreas clínicas concretas.[1] La mayoría de los estudios publicados a nivel hospitalario evalúa el impacto de la actividad farmacéutica en el hospital en su conjunto, sin analizar los resultados obtenidos en diferentes áreas del mismo por separado. Y dado que los fármacos empleados, el perfil de los pacientes y la gravedad de los incidentes varían en las diferentes áreas, las consecuencias clínicas y económicas de las intervenciones de los farmacéuticos clínicos pueden también variar. Hasta la fecha no disponemos de ningún estudio comparativo acerca del impacto clínico y económico de las intervenciones centradas en antiinfecciosos y llevadas a cabo por el farmacéutico en concreto en Unidades de Cuidados Intensivos (UCIs) de hospitales europeos. Por ello, en nuestro centro, que hemos optado por disponer de un farmacéutico clínico en el Área de Cuidados Críticos (ACC), hemos querido analizar el impacto de sus intervenciones en los resultados de los pacientes atendidos en dicha unidad.

Debido a la situación económica actual, resulta prioritario optimizar los recursos de los que dispone el farmacéutico clínico, así como priorizar la atención farmacéutica a aquellos grupos de pacientes que pueden obtener un mayor beneficio. En este sentido, las UCIs abarcan un grupo de pacientes especialmente de interés, debido a la complejidad y gravedad de su situación, entre otros aspectos. Según el estudio

multicéntrico llevado a cabo por Merino *et al.*[2] en UCIs españolas, un 58% de los pacientes presentó al menos un incidente. Todo ello justifica el interés de evaluar el impacto de la actividad del farmacéutico en esta área.

En caso de no poder disponer de un farmacéutico que dé asistencia a todos los pacientes de la UCI, se podrían emplear estrategias para seleccionar aquellos pacientes sobre los que actuar a través de las intervenciones del farmacéutico clínico. Una estrategia podría ser la creación de un modelo de estratificación de pacientes, que permitiera priorizar la atención farmacéutica a aquellos pacientes que presentan un mayor riesgo de sufrir eventos adversos relacionados con medicamentos. Se trataría de una adaptación de la "Pirámide de Kaiser" creada para la clasificación de pacientes crónicos,[3] que constituye un sistema ampliamente utilizado para la estratificación de pacientes. Algunos de los criterios que se podrían incluir en dicho modelo para su adaptación al ámbito hospitalario serían: la presencia de pluripatología y comorbilidades, las alergias, los criterios de gravedad (*p.ej.*: según el *Simplified Acute Physiology Score* 3 (SAPS3)), el número de hospitalizaciones recientes o reagudizaciones de patologías crónicas, la presencia de insuficiencia renal y/o hepática, la polimedicación, el tratamiento con medicamentos de alto riesgo (atendiendo a la lista de medicamentos de alto riesgo para pacientes crónicos (Proyecto MARC)[4]: anticoagulantes orales, antiepilépticos de estrecho margen, inmunosupresores, *etc.*), y el tratamiento con fármacos inhibidores y/o inductores enzimáticos (*p.ej*: amidarona, carbamazepina, azoles, *etc.*), entre otros. Ello permitiría clasificar a los pacientes en base a los criterios anteriormente expuestos, estableciéndose el nivel de riesgo de sufrir acontecimientos adversos que presenta cada sujeto. Y en un segundo escalón, se podrían establecer diferentes niveles de atención farmacéutica según el nivel de riesgo.

Una vez seleccionados los pacientes, por lo que respecta al tipo de intervenciones farmacéuticas, las recomendaciones específicas representan el tipo de intervención más prevalente en los estudios publicados hasta la fecha. El impacto tras este tipo de intervención resulta más inmediato y más objetivo que el resultado que se obtiene tras la educación del farmacéutico a los diferentes profesionales o la implantación de guías y protocolos. Del mismo modo, en la mayoría de estudios de manera frecuente se da la combinación de diferentes tipos de intervenciones farmacéuticas de manera

simultánea, lo que dificulta la posibilidad de analizar el impacto de cada tipo de intervención de forma aislada.

Una de las medidas que permite potenciar el efecto de las intervenciones farmacéuticas consiste en la integración del farmacéutico clínico en el equipo multidisciplinar. Los estudios publicados ponen de manifiesto el mayor beneficio que se obtiene cuando las intervenciones farmacéuticas se realizan trasladado el farmacéutico a la unidad asistencial e integrado en el equipo multidisciplinar de forma adicional o no a la intervención farmacéutica llevada a cabo desde el Servicio de Farmacia de forma centralizada, frente a cuando solamente se realiza la intervención farmacéutica de forma centralizada. Con la integración del farmacéutico en el equipo multidisciplinar se obtuvo una mayor aceptación de las intervenciones por parte del médico,[5] una reducción en la tasa de eventos adversos prevenibles,[6,7] en la frecuencia y duración de errores de medicación,[8] así como en los costes.[9] Esto podría deberse a que tras la participación del farmacéutico en el pase de visita, éste obtiene una visión más global y completa del paciente, que le permite evaluar la prescripción con un mayor conocimiento de la historia médica, alergias, estado de la función orgánica, *etc*. del paciente. Por otro lado, hace posible que la intervención farmacéutica se realice justo en el momento de la prescripción. Además, mediante su presencia física se facilita tanto la transmisión de información como la interacción con el resto de profesionales involucrados en el cuidado del paciente. En la revisión llevada a cabo por Davey *et al.*,[10] se obtuvo que aquellas intervenciones que proveían recomendaciones o *feedback* al médico fueron más efectivas en mejorar la calidad de la prescripción que aquellas que no suministraban dicha información al médico. Por otro lado, la participación activa del farmacéutico en el equipo multidisciplinar también facilita el papel educacional de éste. Todo esto revierte en una optimización de los tratamientos y reducción de los problemas relacionados con la medicación y por tanto, en una mejora en la calidad asistencial.

Desde el punto de vista de los pacientes, la asociación de pacientes del Reino Unido llevó a cabo en 2016 una encuesta para conocer la opinión de pacientes y cuidadores acerca del papel del farmacéutico clínico, en la cual se obtuvo que un 76,9% de los encuestados consideraba beneficiosa la contribución del farmacéutico clínico al equipo

asistencial; y que un 77,5% valoraba de manera positiva la revisión del tratamiento farmacológico por parte del farmacéutico clínico.[11]

Respecto a los tratamientos antimicrobianos en concreto, resulta evidente la relevancia que tiene la integración del farmacéutico clínico en los equipos multidisciplinares involucrados en su manejo. En diversos estudios se ha observado que los antiinfecciosos fueron los fármacos más frecuentemente implicados tanto en errores de medicación[12] como en reacciones adversas a medicamentos.[13] Esto, junto con el actual problema de incremento de la resistencia a antimicrobianos, pone de manifiesto la necesidad de actuar en este ámbito. En concreto en el paciente crítico, el farmacéutico tiene un papel clave en la optimización de los tratamientos, que deben adaptarse a la situación que presenta el paciente en cada momento. Para ello resulta necesario promover la especialización del farmacéutico clínico en el ámbito de infecciones y manejo de antimicrobianos. La labor del farmacéutico especialista en enfermedades infecciosas debería consistir en: optimizar los tratamientos de manera que sean efectivos y seguros, monitorizar la utilización de antimicrobianos y dar *feedback*, crear junto con el resto del equipo multidisciplinar un programa de manejo de antimicrobianos, proveer educación a otros profesionales y participar como miembro en el comité de enfermedades infecciosas.[14]

En el estudio llevado a cabo por la OMS para evaluar las campañas acerca del uso de antimicrobianos desarrolladas en diferentes países se pone de manifiesto el papel clave del farmacéutico en la concienciación acerca del problema de las resistencias, así como en la promoción de un uso racional de los antimicrobianos.[15]

En el análisis que hemos llevado a cabo acerca de las intervenciones sobre antimicrobianos realizadas por el farmacéutico clínico en el Área de Cuidados Críticos de la Clínica Universidad de Navarra se evidencia que las intervenciones más frecuentes han sido: la modificación de la dosis y/o intervalo de dosificación, la suspensión y el cambio a una vía de administración más coste-efectiva; y aquellas que produjeron un mayor impacto económico por intervención fueron el cambio a un antimicrobiano más coste-efectivo, la suspensión del tratamiento y el cambio a una vía de administración más coste-efectiva. Se debería trabajar en potenciar herramientas

para completar algunas de estas intervenciones, lo que permitiría optimizar la labor asistencial del farmacéutico. En concreto, a continuación se proponen algunas de ellas:

- Ayudas para el ajuste posológico de fármacos, por ejemplo en insuficiencia renal y hepática.
- Potenciación de los programas de terapia secuencial.
- Recomendaciones acerca de la duración de tratamientos profilácticos, con alertas en la prescripción para detectar tratamientos que se prolongan más de lo establecido.
- Difusión de evidencia sobre antimicrobianos de primera elección según el tipo de infección basada en criterios de beneficio-riesgo y coste-efectividad.

Respecto a los resultados de los diferentes estudios publicados acerca del impacto de las intervenciones farmacéuticas sobre antimicrobianos, los aspectos más frecuentemente evaluados fueron los relacionados con el tratamiento y/o la prescripción, los clínicos y los económicos. Se obtuvo un impacto significativo de manera más frecuente en los resultados relacionados con el tratamiento y/o la prescripción y en los datos económicos, la frecuencia fue menor en los resultados clínicos.

Respecto al impacto económico de las intervenciones farmacéuticas, la mayoría de estudios sólo analizan los costes directos; en concreto, la mayoría sólo tiene en cuenta la diferencia en el coste de los fármacos antimicrobianos cuando interviene el farmacéutico frente a cuando éste no interviene. Sólo una minoría incluye en el análisis económico el coste que conlleva el tiempo que dedica el farmacéutico clínico a realizar intervenciones.[16-20] Del mismo modo, son muy pocos los estudios que analizan el coste atribuible a eventos adversos.[16,17,21] En la revisión llevada a cabo por Vlayen *et al.*,[22] en la que se analizaba la incidencia y evitabilidad de los eventos adversos que propiciaron ingreso en UCIs, sólo uno de los 27 estudios analizados incluyó el análisis económico de los eventos adversos. Del mismo modo, se observa mucha heterogeneidad entre estudios en lo que se refiere al análisis económico de los eventos adversos,[23,24] lo que dificulta poder realizar una comparación de los resultados obtenidos. Algunos estudios consideran sólo los eventos adversos relacionados con medicamentos, otros los

eventos adversos debidos a medicamentos y procedimientos (cirugías, *etc*.), otros incluyen sólo los eventos adversos graves, otros tanto los eventos adversos graves como los no graves, otros incluyen sólo los eventos adversos debidos a grupos de fármacos concretos (*p.ej*: tratamientos quimioterápicos), otros analizan sólo los eventos adversos ocurridos en urgencias y cuidados intensivos, *etc*. Ciertos eventos adversos como los graves, los debidos a tratamientos quimioterápicos, los acontecidos en pacientes críticos, *etc*. conllevan un impacto económico mayor, lo que debe tenerse en cuenta a la hora de comparar los resultados obtenidos en los diferentes estudios.[23]

Por otra parte, muy pocos estudios incluyen los costes indirectos asociados a un evento adverso, debido a que su análisis presenta mayor complejidad.[23] En la revisión llevada a cabo por Batel *et al*.,[23] todos los estudios analizaron los costes directos asociados a eventos adversos a medicamentos, pero sólo un 7% de los mismos estimó además los costes indirectos.

Fukuda *et al*.[25] llevaron a cabo una revisión con el objetivo de evaluar la transparencia de los estudios publicados acerca de la estimación de costes en evaluaciones económicas sobre programas de seguridad del paciente. Observaron que existe una gran variación entre los diferentes estudios en relación a la transparencia y exactitud de la metodología utilizada para estimar el coste, por lo que la toma de decisiones en base a estos resultados se debe realizar de manera cautelosa.

En lo que respecta a la evaluación económica de las intervenciones sanitarias, en el futuro es necesario obtener un consenso acerca de su metodología,[26] así como emplear términos y definiciones comunes,[25] con el objetivo de reducir las discrepancias. Además, los análisis económicos deben incluir tanto los costes vinculados a los eventos adversos como el coste de la intervención farmacéutica.

Respecto al resto de aspectos evaluados en los estudios, aquellos relacionados con el tratamiento/prescripción (duración del tratamiento, duración del tratamiento por vía intravenosa, dosis apropiada, *etc*.) pueden resultar más fácilmente medibles que los aspectos clínicos (tasa de desarrollo de infecciones, efectividad del tratamiento, eventos adversos, *etc*.), pero en definitiva el objetivo final debe consistir en demostrar el impacto de las intervenciones farmacéuticas en los aspectos clínicos, debido a su

mayor relevancia. Por ello, los estudios que se realicen en el futuro deberían necesariamente incluir resultados clínicos, ya que esto permitiría objetivar el impacto real de las intervenciones farmacéuticas.

Del mismo modo, los estudios deberían analizar el impacto de la intervención farmacéutica en la calidad de vida de los pacientes, así como incluir la perspectiva de los mismos ("*Patient Reported Outcomes*"). Esto permitiría personalizar el tipo de intervención según los diferentes perfiles de pacientes, así como conocer su punto de vista acerca de la utilidad o beneficio de cada tipo de intervención. Cawthon *et al*.[27] llevaron a cabo un estudio basado en encuestas telefónicas con el objetivo de evaluar el beneficio que los pacientes percibían de los diferentes componentes de la intervención farmacéutica (conciliación de la medicación, consejo farmacéutico, ayudas para la adherencia y seguimiento telefónico). La mayoría de los pacientes calificaron de manera muy positiva la información sobre la medicación proporcionada por el farmacéutico previo al alta (72,8% de los pacientes), el haber recibido un documento recogiendo la pauta de tratamiento (69,6%) y el haber recibido una llamada telefónica de seguimiento tras al alta (68,0%). Aquellos pacientes con menor educación sanitaria evaluaron de manera más positiva la intervención farmacéutica. La revisión de Al-Jumah *et al*.[28] demostró que la intervención farmacéutica fue efectiva para mejorar la adherencia de los pacientes a fármacos antidepresivos. Rajesh *et al*.[29] en su estudio observaron que las intervenciones farmacéuticas acerca del tratamiento antirretroviral en pacientes diagnosticados de Virus de la Inmunodeficiencia Humana (VIH), aumentaron de manera significativa el conocimiento acerca del tratamiento antirretroviral y mejoraron la actitud y el pensamiento de los pacientes acerca del mismo. La recogida de estas variables en el ámbito de los pacientes críticos, resulta sin embargo más compleja.

Hasta la fecha, la evidencia acerca del impacto de las intervenciones farmacéuticas sobre aspectos microbiológicos es muy limitada (tasa de erradicación de los patógenos, tasas de resistencia, *etc*.), ya que cambios en este tipo de parámetros son difícilmente atribuibles solamente a las intervenciones farmacéuticas. En relación al caso concreto del análisis del impacto de la adición de antibioterapia inhalada al tratamiento antimicrobiano sistémico en pacientes críticos con infecciones respiratorias, no ha sido

posible analizar resultados microbiológicos, ya que en la mayoría de casos no se disponía de cultivos al finalizar el proceso infeccioso. En el futuro, en la medida de lo posible, los estudios deberían incluir parámetros microbiológicos (erradicación del microorganismo, evolución de la Concentración Mínima Inhibitoria y de la carga microbiológica en el tiempo, aparición de resistencias, *etc*.) para analizar el impacto del farmacéutico a este nivel.

Como ya se ha comentado, la evidencia acerca del impacto de las intervenciones farmacéuticas sobre antiinfecciosos en las UCIs de hospitales es limitada, más aún en centros europeos y/o que cuenten además con un Programa de Optimización del uso de Antiinfecciosos (PROA), y conocer la aportación adicional del farmacéutico clínico a estos programas resulta de interés. Por ello, y dado que en nuestro centro se dan estas condiciones y se registran las intervenciones del farmacéutico y las consecuencias de las mismas en la práctica rutinaria, resultó pertinente analizar esta información con objeto de estimar cuantitativamente el impacto clínico y económico de la actividad del farmacéutico clínico en estas circunstancias. Se realizó un estudio observacional que, a pesar de tener la limitación de ser no controlado, tiene la ventaja de reflejar la práctica clínica diaria, y el registro de los datos no se vió influenciado por la realización del estudio. Los resultados obtenidos han puesto de manifiesto el impacto positivo de la labor del farmacéutico clínico en relación a la optimización de los tratamientos antimicrobianos, que sería necesario confirmar con futuros estudios.

El farmacéutico clínico del ACC además, en conjunto con los equipos médicos, ha impulsado estrategias concretas en relación a antiinfecciosos. En el presente trabajo se ha analizado el impacto de añadir antibioterapia inhalada al tratamiento antimicrobiano sistémico en pacientes críticos con infecciones respiratorias. Dicha estrategia se ha posicionado como clave en el manejo de infecciones respiratorias, sobre todo para conseguir concentraciones eficaces en el lugar de la infección, y también para hacer frente al problema de la multirresistencia. A pesar del carácter exploratorio del estudio observacional que hemos llevado a cabo en nuestro centro, añadir antibioterapia inhalada en pacientes críticos con infecciones respiratorias ha mostrado resultados prometedores en cuanto al impacto en la mejoría clínica de los mismos sin incremento de la toxicidad. Además, constituye un ejemplo de las iniciativas multidisciplinares que

repercuten en una mejora de la calidad asistencial y mejores resultados en los pacientes, al igual que otras intervenciones realizadas por el farmacéutico clínico sobre antiinfecciosos en el ACC.

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5. CONCLUSIONES

1. La evidencia disponible recoge que el farmacéutico, realizando intervenciones específicas relacionadas con la terapia antiinfecciosa de los pacientes, mejora los resultados clínicos y los resultados relacionados con los tratamientos, a la vez que disminuye los costes.

2. En la revisión realizada de los estudios publicados acerca de las intervenciones farmacéuticas sobre antiinfeciosos, un elevado porcentaje de los trabajos que analizaron resultados relacionados con el tratamiento antiinfeccioso o costes obtuvo resultados positivos significativos. Este porcentaje fue inferior en los estudios que analizaron resultados clínicos. Muy pocos estudios evaluaron el impacto microbiológico.

3. En la bibliografía, las recomendaciones específicas dirigidas a pacientes concretos constituyen el tipo de estrategia más prevalente entre las intervenciones farmacéuticas relacionadas con antiinfecciosos. Añadir a éstas el establecimiento de guías o protocolos o sesiones educativas no se ha demostrado que incremente su impacto clínico o económico.

4. La mayor parte de los estudios comparativos publicados que analizan el impacto de las intervenciones del farmacéutico sobre antiinfecciosos en el ámbito hospitalario son de baja calidad y no existen estudios publicados al respecto en unidades de cuidados intensivos europeas.

5. El farmacéutico clínico integrado en el equipo asistencial del Área de Cuidados Críticos de la Clínica Universidad de Navarra, realizando intervenciones relacionadas con antiinfecciosos, tuvo un impacto clínico positivo. Un 96% de sus intervenciones se consideraron importantes con mejora en el cuidado del paciente. Ninguna intervención tuvo un impacto negativo en los pacientes. La aceptación de las intervenciones por parte del médico fue del 98%.

6. Durante un periodo de 5 meses, el farmacéutico clínico detectó 212 problemas relacionados con antiinfecciosos en 114 pacientes, de los cuáles 18 se consideraron errores de medicación. Cada uno de ellos le llevó a la realización de intervenciones.

7. Se estima que estas intervenciones evitan 4,8 € por cada euro invertido en el farmacéutico. Con una reducción del coste en 5 meses de 10.905€, 51 € por cada intervención y 96 € por cada paciente.

8. Las intervenciones del farmacéutico clínico sobre antiinfecciosos en el Área de Cuidados Críticos más prevalentes fueron la modificación de la dosis y/o el intervalo posológico, la suspensión del antimicrobiano y el cambio a una vía de administración más coste-efectiva. Las dos primeras intervenciones se asocian a una mayor reducción del coste. Aunque las intervenciones con mayor ahorro por intervención fueron el cambio a un antimicrobiano más coste-efectivo y la suspensión del antiinfeccioso.

9. En el pequeño estudio observacional realizado para evaluar el impacto de una iniciativa promovida y liderada por el farmacéutico clínico junto al equipo multidisciplinar que atiende al paciente crítico, que consistía en añadir antibioterapia inhalada al tratamiento antimicrobiano sistémico en pacientes con infecciones respiratorias, se observó que esta estrategia está asociada con una mejor respuesta clínica de los pacientes.

10. Los resultados obtenidos en la bibliografía y en nuestro centro confirman el impacto positivo de las intervenciones realizadas por el farmacéutico clínico sobre antiinfecciosos en pacientes críticos. Estos resultados deberían ser completados con estudios comparativos más amplios que analicen otras variables de resultados y permitan identificar las estrategias con mayor impacto, y así mejorar la calidad asistencial y los resultados en los pacientes.