

Arturo Artero¹
Ángel Atienza¹
Sara Correa²
Ian López²
Alejandra Faus²
Francesc Puchades²
Manuel Madrazo²

Ertapenem therapy for pneumonia requiring hospital admission in elderly people

¹Servicio de Medicina Interna, Hospital Universitario Dr. Peset. Universitat de València.

²Servicio de Medicina Interna, Hospital Universitario Dr. Peset. Valencia.

ABSTRACT

Background. Few studies examined ertapenem for the treatment of pneumonia. This study aims to compare ertapenem with other antibiotics commonly used for the treatment of pneumonia requiring hospital admission in elderly patients in daily clinical practice.

Methods. We conducted an observational, retrospective case-control study, between January 2011 and January 2014, in a university hospital. Patients ≥ 65 years of age admitted to the hospital with pneumonia treated with ertapenem were included as cases. A control patient treated with antibiotics other than ertapenem, matched for age and pneumonia severity index (PSI), was enrolled for each case. Hospital mortality was the primary outcome.

Results. A total of 150 patients with a mean age of 84.1 years were studied. Ninety percent of patients had pneumonia PSI grade IV-V and 82.7% had one or more comorbidities. Healthcare-associated pneumonia (HCAP) and aspiration pneumonia were significantly higher in the ertapenem group (66.7% vs. 24.0%, $p < 0.001$ and 73.3% vs. 54.7%, $p < 0.017$, respectively), whereas malignancy was most common in the control group. There was no difference in the hospital mortality rate between ertapenem and control groups (20.0% vs. 20.0%, $p = 0.500$), after adjusting for HCAP, aspiration pneumonia and malignancy. Transfer from hospital to hospital at home was significantly higher in the ertapenem group (25.3% vs. 9.3%, $p = 0.09$).

Conclusions. Ertapenem is as effective as other antibiotics commonly used for the treatment of pneumonia requiring hospital admission in elderly people. Ertapenem is associated with a higher transfer to hospital at home.

Tratamiento con ertapenem de la neumonía que requiere ingreso en el hospital en el paciente anciano

RESUMEN

Introducción. Existen pocos estudios que analicen el tratamiento de las neumonías con ertapenem. El objetivo de este estudio es comparar ertapenem con otros antibióticos usados comúnmente en el tratamiento de pacientes ancianos hospitalizados por neumonía en condiciones de práctica clínica habitual.

Métodos. Estudio observacional, retrospectivo, de casos y controles, realizado entre enero de 2011 y enero de 2014, en un hospital universitario. Se incluyeron como casos a los pacientes de edad ≥ 65 años ingresados por neumonía que fueron tratados con ertapenem. Por cada caso se incluyó un control apareado por edad y *pneumonia severity index* (PSI) tratado con otros antibióticos distintos a ertapenem.

Resultados. Se estudiaron 150 pacientes con una edad media de 84,1 años. Noventa por ciento de los pacientes tuvieron neumonía con PSI grado IV-V y 82,7% tuvieron una o más comorbilidades. Neumonía asociada con los cuidados sanitarios (NACS) y neumonía por aspiración fueron significativamente más frecuentes en el grupo de ertapenem (66,7% vs. 24,0%, $p < 0,001$ y 73,3% vs. 54,7%, $p < 0,017$, respectivamente), mientras que el cáncer fue más común en el grupo control. No se observaron diferencias en la mortalidad entre los casos y controles (20,0% vs. 20,0%, $p = 0,500$), después de ajustar por NACS, neumonía por aspiración y cáncer. El traslado a una unidad de hospitalización a domicilio fue más frecuente en el grupo de ertapenem (25,3% vs. 9,3%, $p = 0,09$).

Conclusiones. Ertapenem es tan eficaz como otros antibióticos comúnmente empleados para el tratamiento de la neumonía en pacientes ancianos que requieren hospitalización. Ertapenem se asoció a una mayor utilización de la unidad de hospitalización a domicilio.

Correspondence:
Arturo Artero
Hospital Universitario Dr Peset Av Gaspar Aguilar 90, 46017 Valencia, Spain.
Tel.: +34 961622457
Fax: +34 961622301
E-mail: arturo.artero@uv.es.

INTRODUCTION

Pneumonia is the leading cause of mortality from infectious diseases in developed countries and it is the ninth leading cause of mortality¹. Both the incidence and severity of pneumonia increase in elderly people. A wide range of microorganisms cause pneumonia, therefore, there is no one antibiotic or combination of antibiotics that is adequate for all cases. From the many antibiotics that have proven useful for the treatment of pneumonia, especially for those severe cases requiring hospital admission, ertapenem offers some advantages on pharmacodynamic and microbiological levels. Ertapenem is a group 1 carbapenem active against most bacteria commonly recovered from community-acquired infections², including pneumonia^{3,4} used as a single daily dose. Ertapenem is not only active against *Streptococcus pneumoniae* and *Haemophilus influenzae*, some of the most frequent causes of community acquired pneumonia, but also against *Enterobacteriaceae* and anaerobes⁵. As is the case for any other β -lactam it is not active against *Legionella*, *Mycoplasma pneumoniae* or *Chlamydia* species, therefore it is sometimes used in combination with other antibiotics active against these bacteria. Ertapenem is one of the β -lactams recommended by current international guidelines^{6,7} for the treatment of community-acquired pneumonia (CAP) and healthcare-associated pneumonia (HCAP) in patients admitted to hospital.

Articles demonstrating the efficacy of ertapenem in treating pneumonia were first published in the 1980's; since that time very few studies⁸⁻¹⁰ have backed up this initial finding, and there is a particular lack of information about its use for the treatment of pneumonia requiring hospital admission in elderly people. These facts motivate us to carry out a retrospective study of the treatment of elderly patients with CAP or community onset HCAP with ertapenem in order to compare its efficacy with other antibiotic regimens.

MATERIAL AND METHODS

Study setting. The Hospital Universitario Dr. Peset is a 531-bed urban tertiary care hospital in Valencia, Spain. It is a referral hospital for a population of 370,000 people. The study was approved by the ethics committee of the hospital.

Study design. We conducted an observational, retrospective case-control study, carried out between January 2011 and January 2014. All patients diagnosed in a consecutive manner with community acquired or community onset healthcare associated pneumonia ≥ 65 years of age and treated with ertapenem (1 g once a day for a minimum of 2 days) were included as cases in this study. A control patient treated with antibiotics other than ertapenem was enrolled for each case. The selection process of cases and controls is detailed in figure 1. The selection of control patients was made by two researchers (AA and IL) without knowledge of either the case patients' goal variables or those of the control patients.

Data collection. Data was obtained from the patients'

electronic medical records. The information collected included: demographic data; underlying illnesses; clinical, radiological and laboratory information necessary to classify patients according to HCAP¹¹, Pneumonia Severity Index (PSI)¹² and aspiration pneumonia¹³; nursing home residence; antibiotic treatment; microbiological tests, hospital mortality; length of hospital stay; admission to hospital at home and readmission within 30 days. In order to have thorough information about antibiotic treatment in the three months previous to hospital admission the authors also revised the patient's general practitioner's electronic prescription records.

The primary outcome measured was hospital mortality. Other prognostic variables analyzed were length of hospital stay, transfer to hospital at home and readmission within 30 days.

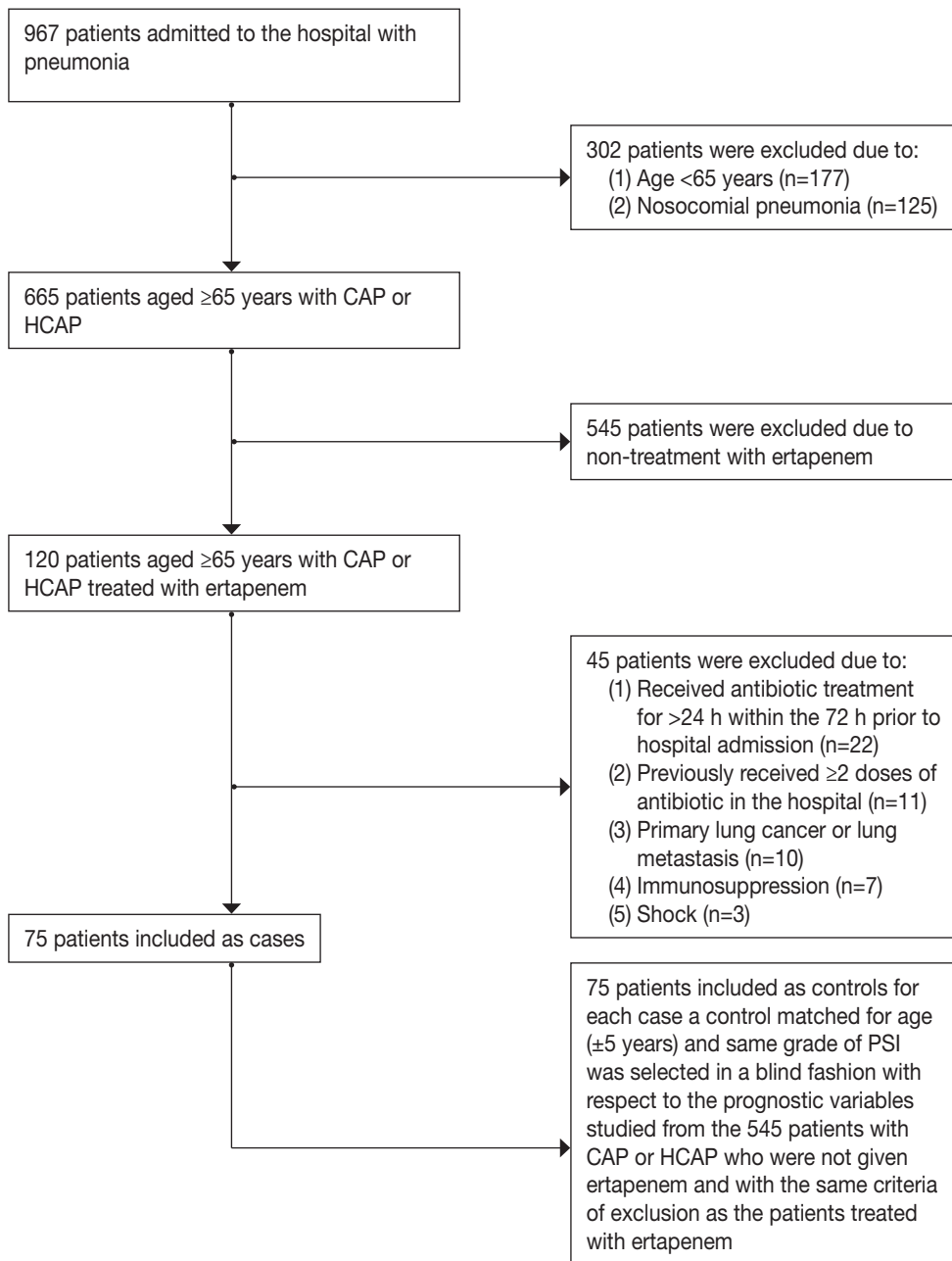
Literature search. A review of the literature for the treatment of pneumonia with ertapenem was done using PubMed with ertapenem and pneumonia as search terms. In addition, a manual search was conducted through reference lists of publications identified in the initial search.

Statistical analysis. To compare variables between the case and control groups we used the chi-squared test for categorical variables and the Student's t-test for continuous variables. Logistic regression was used to test the association between the prognostic variables (hospital mortality, length of hospital stay, transfer to hospital at home and readmission within 30 days) within the groups of case and control while adjusting for covariates (HCAP, aspiration pneumonia and cancer). Statistical significance was set at value of $p < 0.05$. SPSS v22.0.0 software (IBM Corp., Somers, NY) was used to perform statistical analyses.

RESULTS

Demographic data as well as clinical characteristics of the 150 patients included, 75 cases and 75 control patients, are shown in table 1. The mean age of the cohort was 84.16 ± 6.55 years, 88 patients (56.0%) were female, 136 (90.7%) had PSI grade IV or V and 124 (82.7%) had one or more comorbidities. While aspiration pneumonia and HCAP were significantly higher in the ertapenem group (66.7% vs. 24.0%, $p < 0.001$ and 73.3% vs. 54.7%, $p < 0.017$, respectively), no differences were found for Charlson's index or nursing home residence. Malignancy was the only comorbidity that was significantly higher in the control group (5.3% vs. 20.0%, $p = 0.007$).

The comparison of the patterns of antibiotic treatment between cases and controls is shown in table 2. No differences were observed between ertapenem and control groups for monotherapy treatment, length of antibiotic treatment, length of intravenous antibiotic treatment or sequential treatment. Ertapenem was given as monotherapy in 59 (78.7%) cases. The antibiotics associated with ertapenem were levofloxacin in 8 cases, vancomycin in 3 cases and in one case each with azithromycin, clindamycin, ceftriaxone, amoxicillin clavulanate and ciprofloxacin. Monotherapy was used in the control group in



Abbreviations: CAP, community acquired pneumonia; HCAP, healthcare-associated pneumonia; PSI, pneumonia severity index.

Figure 1 | Flow chart of the case and control selection process and specific reasons for exclusion from the study.

53 (70.7%) cases. The antibiotics used in monotherapy were: levofloxacin in 23 cases, meropenem in 11 cases, amoxicillin clavulanate in 9 cases, ceftriaxone in 8 cases, and cefuroxime and piperacillin-tazobactam in 1 case. Twenty-two (29.3%) patients were treated with antibiotic combinations in the control group: meropenem and levofloxacin in 6 cases, ceftriaxone and azithromycin in 6 cases, ceftriaxone and levofloxacin in 2

cases, meropenem and vancomycin in 2 cases, levofloxacin and clindamycin in 2 cases, and in one case each with levofloxacin and aztreonam, levofloxacin and amoxicillin clavulanate, levofloxacin and vancomycin and ceftriaxone and clindamycin.

Hospital mortality was 7.1% in PSI-III class, 14.6% in PSI-IV class and 31.5% in PSI-V class (p = 0.025). There was no dif-

Table 1 Comparison of the epidemiological and clinical characteristics of 150 patients with pneumonia treated with ertapenem or other antibiotics (controls).

	Total (N = 150)	Ertapenem (N = 75)	Controls (N = 75)	P value
Age, years, mean \pm SD ^a	84.16 \pm 6.55	83.92 \pm 7.73	84.41 \pm 6.40	0.750
Female gender, N (%)	83 (55.3%)	42 (56.0%)	41 (54.7%)	0.870
Health care associated pneumonia, N (%)	96 (64.0%)	55 (73.3%)	41 (54.7%)	0.017
PSI ^a , N (%)				
Class III	14 (9.3%)	7 (9.3%)	7 (9.3%)	1,000
Class IV	82 (54.7%)	41 (54.7%)	41 (54.7%)	
Class V	54 (36.0%)	27 (36.0%)	27 (36.0%)	
Nursing home residence, N (%)	42 (28.0%)	26 (34.7%)	16 (21.3%)	0.069
Aspiration pneumonia, N (%)	68 (45.3%)	50 (66.7%)	18 (24.0%)	<0.001
Charlson index \geq 7, N (%)	58 (38.7%)	24 (32.0%)	34 (45.3%)	0.094
Three months previous antibiotic therapy, N (%)	72 (48.0%)	39 (52.0%)	33 (44.0%)	0.327
Underlying illness, N (%)				
Congestive heart failure	41 (27.3%)	17 (22.7%)	24 (32.0%)	0.200
Pulmonary disease	24 (16.0%)	13 (17.3%)	11 (14.7%)	0.656
Malignancy	19 (12.7%)	4 (5.3%)	15 (20.0%)	0.007
Chronic kidney diseases	23 (15.3%)	7 (9.3%)	16 (21.3%)	0.041
Liver disease	3 (2.0%)	3 (4.0%)	0 (0.0%)	0.245
Cerebrovascular disease	33 (22.0%)	19 (25.3%)	14 (18.7%)	0.324
Diabetes mellitus	45 (30.0%)	21 (28.0%)	24 (32.0%)	0.593
One or more diseases	124 (82.7%)	65 (86.7%)	59 (78.7%)	0.196
Patients with pathogen identified, N (%)	14 (9.3%)	5 (6.7%)	9 (12.0%)	0.262

PSI: Pneumonia Severity Index. ^a Variables used to match the controls

ference in the hospital mortality rate between ertapenem and control groups (20.0% vs. 20.0%, $p = 0.500$), after adjusting for HCAP, aspiration pneumonia and malignancy. Hospital mortality in patients with aspiration pneumonia and in patients with nursing home residence were 24.0% vs. 27.8% and 15.5% vs. 31.3% in the ertapenem group and in the control group, respectively ($p = 0.751$ and $p = 0.265$). Transfer from hospital to hospital at home was significantly higher in the ertapenem group (25.3% vs. 9.3%, $p = 0.09$), while there were no differences in length of stay at hospital and readmission within 30 days (table 3). Length of hospital stay was not different between cases and controls neither in the cases overall (mean = 7.48 ± 3.89 and 7.29 ± 5.03 days, $p = 0.80$, respectively) nor in the subgroup of patients who were transferred from hospital to hospital at home (mean = 7.73 ± 3.89 and 11.00 ± 4.69 days, $p = 0.87$, respectively). Only one patient from the control group was transferred to the intensive care unit.

An aetiology of pneumonia was determined in 14 (9.3%) cases, 6.7% in the ertapenem group and 12.0% in the control group ($p = 0.262$). The microorganisms identified were: *S. pneumoniae* ($n = 10$), *Staphylococcus aureus* ($n = 1$),

Pseudomonas aeruginosa ($n = 1$), *Escherichia coli* ($n = 1$) and *Citrobacter* spp. ($n = 1$). *S. pneumoniae* was identified by detection of capsular polysaccharide antigen in urine in all 10 cases and also by isolation in sputum in 1 case. Other microorganisms were identified by isolation in sputum. No presence of bacteraemia was detected in any case. Two patients with pneumonia caused by *S. pneumoniae* died, the two of them in the control group (one case treated with cefuroxime and one with amoxicillin). One further patient from the control group with *Citrobacter* spp. identified in sputum died after 13 days of treatment with piperacillin-tazobactam. In the case group, one patient with isolation of methicillin resistant *S. aureus* in sputum was treated with ertapenem and levofloxacin and died after 7 days of treatment.

DISCUSSION

This study demonstrates that ertapenem is as effective as other antibiotics commonly used to treat pneumonia in elderly people requiring hospital admission, even

though it is more frequently used in severe conditions such as healthcare-associated pneumonia and aspiration pneumonia. Another interesting finding is that patients who are treated with ertapenem have a significantly higher rate of transfer to hospital at home.

The population studied is a good reflection of the typical elderly patient admitted to hospitals with pneumonia in developed countries in daily clinical practice, generally characterized by very old age and several comorbidities. The patients studied, with a mean age of 84.5 years, are older than the population of previous studies of ertapenem therapy for pneumonia in elderly people¹⁰⁻¹⁴. Besides, our patients also have a higher proportion of underlying illnesses (82.1%), mostly congestive heart failure and pulmonary diseases.

In this study cases were matched to controls by age and severity, determined by PSI, however, three clinical characteristics are statistically different between case and control groups. First, aspiration pneumonia, which usually implies a more severe disease with a longer hospital stay¹⁵, is more common in patients treated with ertapenem. Second, HCAP, which has a higher mortality and may be caused by more resistant

Table 2 Comparison of the patterns of antibiotic therapy among patients treated with ertapenem and those who received other antibiotics (controls).

Variables	Ertapenem	Controls	P value
Monotherapy, No. (%)	59 (78.7%)	53 (70.7%)	0.260
Duration of therapy, days (mean \pm SD)	10.78 \pm 5.30	12.18 \pm 4.90	0.284
Duration of IV antibiotic therapy, days (mean \pm SD)	8.29 \pm 5.06	5.97 \pm 4.35	0.288
Sequential antibiotic therapy, No. (%)	28 (37.3%)	26 (34.7%)	0.734

Table 3 Comparison of prognostic factors between patients who received ertapenem and those who received other antibiotics (controls).

Variables ^a	Ertapenem	Controls	P value	OR (95% CI)
Hospital mortality, No. (%)	15 (20.0)	15 (20.0)	0.500	0.72 (0.28 - 1.84)
Length of hospital stay < 7 days, No. (%)	34 (45.3%)	41 (54.7)	0.295	1.53 (0.68 - 3.40)
Transfer to hospital at home, No. (%)	19 (25.3)	7 (9.3)	0.009	4.68 (1.46 - 14.99)
Hospital readmission within 30 days, No. (%)	11 (14.7)	7 (9.3)	0.417	1.59 (0.51 - 4.88)

^aEvery variable was adjusted for health care associated pneumonia, aspiration pneumonia and malignancy.

OR = odds ratio; CI = confidence interval

microorganisms¹⁶⁻¹⁷, is also more common in patients treated with ertapenem. Third, malignancy, on the other hand, is more common in the control group. In order to avoid influence of these variables on prognostic factors every evaluated outcome was adjusted to them. Nursing home residence is slightly more common in the ertapenem group in this study without being statistically significant. A previous study of CAP found that ertapenem showed significantly higher clinical response in patients coming from nursing homes¹⁰. We do not find this association but due to the limited number of cases in our study it is not possible to establish a conclusion.

We analyze hospital mortality as the primary outcome and we find that ertapenem, in association with other antibiotics in 21.3% of cases, is as effective as other antibiotics usually used in clinical practice – mainly levofloxacin, meropenem, ceftriaxone and amoxicillin clavulanate – for the treatment of pneumonia (hospital mortality of 20.0% both in the ertapenem and control groups; $p = 0.504$). This high mortality rate, both in the ertapenem and control groups, may be due to the fact that most patients included in the study have severe pneumonia (PSI class IV or V in 90.7%) and most of them were very old and with comorbidities. Besides, treatment restrictions could have been applied to our patients as is suggested by the fact that only one patient was transferred to an intensive care unit. Due to the retrospective design of this study, clinical response based on signs and symptoms along with absence of progressive infiltration on chest X-ray is not analyzed given that some information necessary for its evaluation may not have been available in the medical records.

Another relevant finding of this study is that ertapenem

is associated with a greater use of hospital at home (25.3% vs. 9.3%). We do not know why patients in the ertapenem group have a higher rate of transfer to hospital at home, but we suggest that the once-a-day intravenous or intramuscular administration of ertapenem makes it more convenient and suited for use in hospital at home than other antibiotics that need to be administered twice or more times a day. If this increase in transfer to hospital at home were confirmed in future studies, it would represent the potential for significant savings in treatment cost given that the greatest cost in treating pneumonia lies in the cost of hospitalization¹⁸. We found that patients in the ertapenem group had a longer time of IV treatment than the control group (mean = 8.29 vs. 5.97 days), although this difference was not statistical-

ly significant. This finding was not due to a lower proportion of sequential treatment as shown in table 2. We suggest that this could be due to the fact that the patients with aspiration pneumonia, who usually require a long period of IV antibiotic treatment, were selected for ertapenem treatment.

Over 90% of the patients were treated without knowledge of the aetiology of pneumonia, mainly due to the difficulty of obtaining sputum samples from this profile of patients, and therefore it is not possible to evaluate the adequacy of the empiric antibiotic treatment according to susceptibility of the isolated microorganisms. A broad-spectrum antibiotic, such as ertapenem, may be the most appropriate choice for treating these patients due to the fact that they are a population with a high proportion of severe pneumonia (PSI score grade IV or V = 90.1%), aspiration pneumonia and HCAP. Broad-spectrum antibiotics are indicated in most patients with aspiration pneumonia since *S. pneumoniae*, *S. aureus*, *H. influenzae* and *Enterobacteriaceae* predominate in patients with community acquired aspiration pneumonia and in most cases no microorganism is identified in real clinical practice¹⁹. Previously, it had been accepted that HCAP is caused by a higher number of resistant microorganisms¹⁶⁻²⁰, however, some recent studies did not find evidence of a higher rate of resistant microorganisms in such cases^{21,22}. Ertapenem is active against *Enterobacteriaceae* and anaerobes but it is not active against methicillin-resistant *S. aureus* (MRSA) and *P. aeruginosa*. One case with isolation of MRSA in sputum was treated with ertapenem with an unsuccessful result, while no isolation of *P. aeruginosa* was obtained. *P. aeruginosa* is an uncommon cause of community acquired pneumonia unless there are some conditions such as chron-

ic lung disease or neutropenia²³. However, we do not know if these resistant microorganisms could have caused pneumonia in some of our other patients and, logically, ertapenem should not be used in cases in which these microorganisms are considered causative.

This investigation has several limitations. This is a retrospective study with data limited to the documentation in the electronic medical records and with a relative small number of patients. The study was carried out in a single institution, therefore the data obtained may not be applicable to other settings. Lastly, most of the pneumonias in the study lack identification of a microorganism, making the evaluation of infections caused by multi-drug resistant microorganisms impossible.

In conclusion, these findings support the use of ertapenem for the treatment of elderly people with CAP or HCAP requiring hospital admission. Ertapenem is as effective as other antibiotics commonly used to treat these conditions and, interestingly, ertapenem is associated with a higher transfer to hospital at home. We find a tendency to use ertapenem in patients with HCAP and aspiration pneumonia. Further studies in clinical practice are needed to validate these findings in other settings.

CONFLICTS OF INTEREST

None of the authors has any conflicts of interest to declare.

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