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Effectiveness and safety of outpatient parenteral antimicrobial therapy in acute exacerbation of chronic obstructive pulmonary disease

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Summary

Aim: We analysed the effectiveness and safety of outpatient parenteral antibiotic therapy (OPAT) in acute exacerbation of chronic obstructive pulmonary disease (AECOPD) in patients admitted to home hospitalisation units (HHU).

Methods: Retrospective multicentre study of patients with AECOPD included in the Spanish OPAT Registry during 2 years period.

Results: Twenty-seven hospitals included 562 episodes in 361 patients diagnosed COPD GOLD III-IV. The most frequently isolated pathogen was *Pseudomonas aeruginosa* (38%) and the most frequently used antibiotic was piperacillin-tazobactam (20%). The effectiveness of OPAT defined as the rate of improvement or recovery was 93.4%. The safety of OPAT defined as no adverse drug events and no infectious or catheter-related complications was 89.3%. Moreover, the risk of hospital readmission was not greater in patients with AECOPD aged >80 years. No differences in the effectiveness or safety were observed when OPAT was administered by patients and/or caregivers.

Conclusion: Patients with AECOPD who require parenteral antimicrobial therapy can be managed effectively and safely in HHU, avoiding hospital stays, readmissions and complications.

1 | INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a frequent cause of morbidity and mortality in developed countries. According to the World Health Organization, COPD is currently the fourth leading cause of death worldwide, and it is estimated to become the third by 2030.

The overall prevalence of COPD in adults aged 40-80 years old in Spain is estimated at 10.2%, although the prevalence study (EPISCAN) found wide variation among regions.[1]

Chronic obstructive pulmonary disease poses a serious public health issue, generating high consumption of financial and health-related resources. The costs amount to 2% of the annual Health Budget and 0.25% of the gross domestic product. In Spain, 68% of the annual cost of treating COPD is spent on hospitalisation.[2] Chronic obstructive pulmonary disease exacerbations contribute to health deterioration, affecting disease progress and increasing death risk. In addition, a direct consequence is a high demand for assistance, estimated at 10%-12% of all primary healthcare consultations in Spain, between 1% and 2% of visits to the emergency room, and almost 10%

of medical admissions.[3] On average, patients with COPD experience 1-4 exacerbations per year.[4] Alternatives to conventional hospitalisation can be useful and efficient COPD exacerbations. Home hospitalisation units (HHUs) stand out as an alternative assistance care.

An HHU is an organisational model able to provide patients with hospital management, medical care and nursing care in their homes. Experts consider HHUs are beneficial for the treatment and management of patients with acute exacerbation of chronic obstructive pulmonary disease (AECOPD)[5] HHUs can avoid nosocomial infections; improve the effectiveness of treatments such as oxygen therapy, mechanical ventilation and home rehabilitation; and strengthen adherence to treatments for chronic diseases. Furthermore, HHU shortens hospital stays and reduces stress in patients and their relatives, while increasing quality of life by making patients the centre and focus of their own treatment.[6]

Between 50% and 70% of AECOPD episodes are infection-related, especially in patients with severe COPD and those with bronchiectasis, who require long-term hospitalisation for parenteral antimicrobial therapy.[7,8]

Outpatient parenteral antimicrobial therapy is an alternative to hospital-delivered parenteral microbial therapy, and HHU is the main healthcare resource for administering and controlling OPAT. Several studies have shown that OPAT is effective and safe.[9-11] However, few studies have investigated its safety and effectiveness on AECOPD. This study aimed to assess the effectiveness and safety of OPAT in patients with AECOPD managed by HHUs.

What's known

Chronic obstructive pulmonary disease (COPD) poses a serious public health issue, generating high consumption of financial and health-related resources. Patients with COPD experience 1 to 4 exacerbations per year. Alternatives to conventional hospitalisation can be useful and efficient in treating COPD exacerbations. Outpatient parenteral antimicrobial therapy (OPAT) is an alternative to hospitalisation, and home hospitalisation units are the main resource for administering and controlling OPAT. Few studies have analysed the effectiveness and safety of OPAT in AECOPD.

What's new

Patients with AECOPD requiring parenteral antimicrobial therapy can be managed in home hospital units effectively and safely, avoiding hospital stays, readmissions and complications. Patient participation in administering OPAT does not reduce safety or effectiveness.

2 | METHODS

2.1 | Spanish OPAT registry and AECOPD

We carried out a multicentre, retrospective study of a group of patients diagnosed with AECOPD because of respiratory infection between March 2013 and February 2015. We used cases included in the Spanish Group of Outpatient Parenteral Antimicrobial Therapy Registry (Spanish OPAT Registry) as a source. Spanish Agency of Medicinal Products and Medical Devices and different hospital's Ethics Committee approved the Spanish OPAT Registry. All patients included in the study provided written informed consent.

The OPAT Registry is an online database from 27 Spanish hospital centres in the public network with HHU.[12] Patients with AECOPD were chosen. All patients included in the study had spirometry confirming COPD. Almost all patients were COPD GOLD III and IV GOLD (Global Iniciative for Chronic Obstructive Lung Disease) (FEV1 30%-50% and FEV1 < 30%), although they are exceptional cases GOLD II (the maximum value of FEV1 was 52%.).

Acute exacerbation of chronic obstructive pulmonary disease is defined as an acute episode of clinical instability that occurs during the natural course of the disease and is characterised by a sustained worsening of respiratory symptoms that goes beyond daily variations. The main symptoms are worsening dyspnoea, cough, increased volume and/or changes in the colour of the sputum. All patients with AECOPD met criteria for infectious exacerbation including positive sputum culture collected when possible and for parenteral antibiotic therapy. All patients continued usual standard therapy (parenteral steroids, aerosol therapy and home oxygen therapy) recommended by the Spanish COPD consensus guidelines (GesEPOC).[13] Because Pseudomonas species are often resistant to oral antibiotics, the GesEPOC recommends parenteral antibiotics for COPD patients undergoing more than 4 cycles of antibiotic treatment in the last year and using oral steroids, FEV1 < 50% (GOLD III and IV), significant presence of bronchiectasis, or previous isolation of Pseudomonas in stable-phase sputum or in a previous exacerbation. Thus, after evaluation by a hospital physician patients included in this study received parenteral antibiotics, which were started empirically until sputum culture results became available.

2.2 | Home hospitalisation unit

Although all patients met the criteria for hospitalisation for AECOPD, not all spent time in the conventional hospital before admission to the HHU. Patients were referred to HHUs after confirmation that they met the criteria for admission: confirmed diagnosis, medical stability, presence of a main caregiver and consent of both patient and caregiver.

Home hospitalisation units teams comprised multidisciplinary healthcare professionals, including specialist physicians (mainly from internal medicine, emergency medicine, geriatrics and pneumology) and nurses with extensive hospital experience.

The criteria were used in accordance with the national guide on procedure HHU consensus, supported by the Spanish Society of Home Hospitalisation Units (SEHAD)[14] according to the clinical judgement of the staff physicians. To be eligible for HHU, patients had to have a suitable level of awareness, be haemodynamically stable, and not have severe fluid and electrolyte imbalances or respiratory acidosis. Social

criteria for eligibility were availability of telephone contact, residence within the hospital's referral area, availability of a home caregiver, adequate family support, and suitable social, familial, and hygienic conditions at home. Participation in the HHU program was voluntary and involved no costs for patients.

2.3 | OPAT administration

Outpatient parenteral antibiotic therapy was administered using standard clinical practices following the IDSA guidelines.[15] To receive HHU care and OPAT in our study, patients had to (i) have an infectious process defined by clinical and analytical criteria (with or without microbiological studies); (ii) require intravenous antibiotic therapy; (iii) have venous access with the appropriate calibre and location for the type of medication and the predicted duration of the intravenous antibiotic therapy; (iv) have adequate family support (suitable level of understanding and collaboration of both patient and caregiver); (v) undergo HHU training provided by nursing staff beforehand; and (vi) be reachable by telephone and reside within the hospital's referral area.

Antibiotics were infused by single-use continuous infusion elastomeric pumps, electronic pumps or gravity infusion. Prescribing physicians took into account the stability of the antibiotic preparation at both room temperature and under refrigeration (2-8°C) after reconstitution, following the protocol recommended in the Spanish Society of Internal Medicine's OPAT guidelines.[16] When necessary, antibiotics were refrigerated during transport and in patients' homes. Patients were visited at home daily or every 48 hours by HHU physicians and nursing teams, who supervised the treatment and condition of the venous access. Moreover, patients were able to receive help by telephone 7 days a week. The nursing staff conducted a training session on OPAT at the hospital for patients and caregivers, and confirmed that there were no adverse effects after the first dose. OPAT was recommended by the medical departments that requested the transfer (mainly pneumologists) and approved by HHU physicians.

2.4 | Variables and statistical analysis

Baseline demographic and clinical characteristics were evaluated: age, sex, length of hospital stay prior to HHU admission, referring department, FEV1 (%), FVC (%) and FEV1/FVC (%) ratio and Charlson comorbidity score.

We recorded the type of venous access and whether patients and/or caregivers diluted the medication and/or connected and disconnected the venous catheter and whether they did so with or without the help of the nursing staff (self-dilution and self-handling).

We also recorded the microorganisms isolated, antimicrobial drugs administered, early readmission, medical complications, adverse effects and complications associated with venous access. Finally, we recorded the length of stay in the HHU.

All patients were followed up in their homes for 1 month after completing OPAT, and any complications during this time were recorded. In addition, 2-4 weeks after hospital discharge, patient's clinical status, resolution of respiratory infection and the need for home oxygen therapy were assessed in a follow-up visit us access.

Outpatient parenteral antibiotic therapy was considered effective when there was a favourable clinical response, defined as the absence of medical complications — haemodynamic stability; absence of fever; improved laboratory findings (blood count, acute phase reactants) — and absence of signs of acute disease on chest imaging, no emergency visits because of clinical deterioration, returning to the basal clinical situation and absence of hospital readmissions, although positive sputum culture may have persisted. We considered the patient recovered when there was a favourable clinical response and sputum culture was negative.

Outpatient parenteral antibiotic therapy was considered safe when there were no catheter-related complications, no adverse drug events and no infection-related complications.

For the statistical analysis, quantitative variables were expressed as means and standard deviations, and qualitative variables were expressed as frequencies and percentages. Univariate analyses included $\chi 2$ tests and Fisher's exact test, as appropriate. Significance was set at $P < .05$. SPSS version 18 (IBM, Armonk, NY, USA) was used for all analyses.

To study hospital readmissions for poor control of AECOPD during HHU follow-up or within 30 days after HHU discharge, we used multivariate logistic regression, with readmissions as the dependent variable and the type of parenteral antimicrobial therapy, Charlson Index, age >80 years, pseudomonas infection and complications of AECOPD as independent variables.

3 | RESULTS

3.1 | General characteristics of patients

During the study period, a total of 5423 patients were included in the Spanish OPAT Registry, and these patients underwent 7108 OPAT treatments. We selected the 361 patients diagnosed with AECOPD (age, 75 ± 11 years; 285 (79%) men); these patients underwent 562 OPAT treatments. Table 1 reports the characteristics of the patients included in the study. The Charlson comorbidity score was ≥3 in 48% of the patients; values ≥3 are considered high.[17] Most patients were admitted to the HHU without being hospitalised on

TABLE 1 General characteristics of patients

Variables	Results
Mean age, in years	75 ± 11.45
Sex (men/women)	285 (79%)/76 (21%)
Charlson Index ≥3	48%
Mean FEV1	38% ± 14
Mean FEV1/FVC	62% ± 13
Mean HHU stay, in days	15.9 ± 12.7
Mean ward stay, in days	4.6 ± 7.6
Community infection	500 (84%)

HHU, home hospitalisation units. FEV1 (Forced Expiratory Volume in 1 Second) , FVC (Forced Vital Capacity)

the wards; among those referred to the HHU from the wards, the mean stay in the hospital before referral was 4.6 ± 7.6 days. The mean HHU stay was 15.9 ± 12.7 days. Most infections (84%) were community-acquired, although 11% infections were acquired in hospitals or nursing homes. Table 1 summarises the characteristics of AECOPD.

Patients were referred to the HHU through various pathways (Table 2). A total of 219 (38.9%) patients were referred from conventional hospital wards; 100 (17.7%) of these were referred from pneumology departments, accounting for 45.6% of all referrals from hospital wards. More than a quarter (27%) of all patients admitted to the HHU were referred from emergency rooms, thereby avoiding admission to conventional wards. Most of the remaining patients were referred from day hospitals, nursing homes and outpatient clinics (Table 2).

3.2 | Microorganisms

The most frequently isolated microorganism was *Pseudomonas aeruginosa* (n = 212; 37.7%). Other microorganisms were *Escherichia coli* (4.6%), *Staphylococcus aureus* (3.0%), *Stenotrophomonas maltophilia* (2.3%), and the following others with <2% frequency: *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Klebsiella pneumoniae* and *Serratia marcescens*. In 36.5% of cases, no microorganisms were isolated. Sputum analysis (Gram staining and cultures) is especially indicated to determine the type of microorganism in patients with severe, repeated exacerbations to ensure appropriate antibiotic coverage. However, it is not easy to obtain optimal cultures from all patients, so no microorganisms are isolated in about one-third of cases.[13]

TABLE 2 Source of referrals for outpatient parenteral antibiotic therapy

	Episodes (n %) (n = 562)
Source of referral	
Hospitalisation ward	219 (38.9)
Emergency department	152 (27)
Day hospitals	63 (11.2)
Outpatient clinics	43 (7.6)
Nursing homes	14 (2.4)
Other areas*	71 (12.9)
Referring hospital ward	
Pneumology	100 (17.7)
Internal medicine	80 (14.2)
Geriatrics	7 (1.2)
Other hospital departments**	32 (5.8)

*Short Stay Unit (2.3%), primary care at home (5.3%), another hospital (4.1%), other areas (1.2%).

**Cardiology (0.2%), palliative care (0.2%), infectious diseases (0.4%), haematology (0.2%), nephrology (0.2%), medical oncology (0.7%), others (3.9%).

TABLE 3 Antibiotics used in outpatient parenteral antibiotic therapy for acute exacerbation of chronic obstructive pulmonary disease

Parenteral antimicrobial therapy (n = 562)	n	%
Piperacillin-tazobactam	115	20.5
Ceftazidime	68	12.1
Ceftriaxone	64	11.4
Ertapenem	57	10.1
Cefepime	46	8.2
Levofloxacin	45	8
Amikacin	45	8
Meropenem	41	7.3
Others*	81	14.4

*Amoxicillin-Clavulanate,[3] Azithromycin,[5] Aztreonam,[16] Ciprofloxacin,[8] Colistin,[12] Cotrimoxazole,[6] Imipenem-cilastatin,[11] Linezolid,[1] Penicillin G Sodium,[1] Teicoplanin,[1] Tigecycline,[2] Tobramycin,[13] Vancomycin.[2]

3.3 | Type of drugs, catheter and infusion

In order of frequency, the most widely used parenteral antimicrobial therapy was piperacillin-tazobactam, with a total of 115 episodes (20.5%), followed by ceftazidime with 68 (12.1%), ceftriaxone 64 (11.4%), ertapenem 57 (10.1%), cefepime 48 (8.2%), levofloxacin 45 (8%), amikacin 45 (8%) and meropenem 41 (7.3%) (Table 3).

Most catheters used for OPAT administration were peripheral (77.5%), followed by peripherally inserted central catheters (14.9%) and central lines (1.4%). The most frequently used method of infusing drugs was gravity infusion (51.6%), followed by elastomeric pumps (27%), electronic pumps (16%) and others (Table 4).

3.4 | Patient/caregiver participation in OPAT administration

To evaluate the effectiveness and safety of self-administration of OPAT, we assessed the involvement of patients and/or caregivers. The patient and/or caregiver participated in the dilution of the medication (self-dilution OPAT) in 19.2% of cases, either with the help of the nursing staff or without, and the patient and/or caregiver connected and disconnected the venous catheter with or without the help of the nursing staff (self-handling OPAT) in 45.6% of cases (Figure 1).

In most (56.4%) cases, OPAT was administered in patients' homes more than once a day, as the most frequently used antibiotic, piperacillin-tazobactam, is usually administered every 6-8 hours.

3.5 | Effectiveness and safety of OPAT

Regarding effectiveness, the outcome was favourable in 93.4% of cases at discharge from the HHU. Moreover, there were no medical complications, no emergency visits because of clinical deterioration and no hospital readmissions. Four (1.1%) patients died at home and 20 (5.5%) visited the emergency room; 9 patients of whom were

TABLE 4 Type of catheter and type of infusion used in outpatient parenteral antibiotic therapy for acute exacerbation of chronic obstructive pulmonary disease

	Peripheral line	Peripherally inserted central catheter	Central line	Others
Type of venous catheter (n %)	436 (77.5%)	84 (14.9%)	8 (1.4%)	34 (6%)
	Gravity	Elastomeric pump	Electronic pump	Others
Infusion type (n %)	290 (51.6%)	152 (27%)	90 (16%)	30 (5.4%)

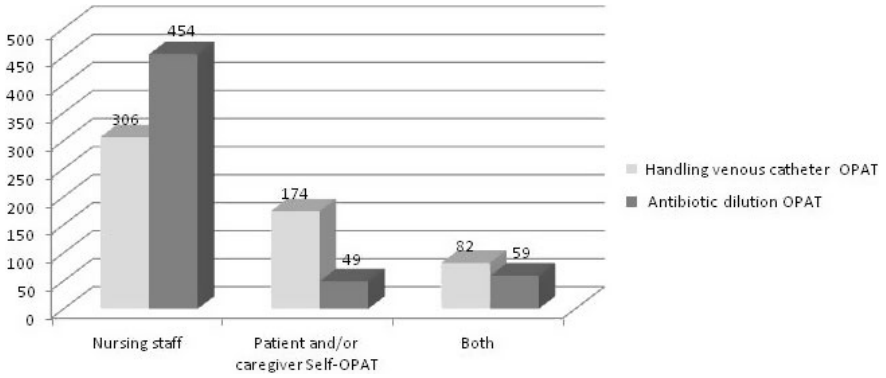

FIGURE 1 Patient participation in administering outpatient parenteral antibiotic therapy for acute exacerbation of chronic obstructive pulmonary disease (n = 562)

readmitted to hospital because of poor control of respiratory infection, defined as persistence or reoccurrence of symptoms despite appropriate treatment. Moreover, 15.7% of patients were readmitted within 30 days of discharge from the HHU.

No differences were found in the effectiveness among patients with high (≥3) and low (<3) Charlson index (*P* = .336). Neither were there differences either in the isolation of *P. aeruginosa*, the most frequent bacteria in severe AECOPD (*P* = .593). There was no apparent relationship between effectiveness and the rest of isolated pathogens.

Outpatient parenteral antibiotic therapy was safe in 89.3% of patients. The main reasons for readmission or termination/modification of treatment were worsening of COPD (n = 32; 5.7%), catheter-related complications (n = 15; 2.7%) and adverse effects (n = 13; 2.3%). The most common adverse effects were urticaria (n = 3), diarrhoea (n = 3) and kidney failure (n = 3); phlebitis was the most frequent catheter-related complication (n = 10).

The safety of OPAT did not differ between patients with high (≥3) and low (<3) Charlson index scores (*P* = .522) or between those in whom *P. aeruginosa* was isolated and those in whom other pathogens or no pathogens were isolated (*P* = .324).

No differences were observed between patient/caregiver took part in the dilution of the parenteral antimicrobial therapy (self-dilution OPAT) and nurse-dilution OPAT in effectiveness (*P* = .144) or safety (*P* = .193). Likewise, there were no differences between self-handling OPAT and nurse-handling of the venous catheter (connection and disconnection when administering the medication) in effectiveness (*P* = .689) or safety (*P* = .417) (Table 5).

In the analysis of hospital readmissions poor control of AECOPD during follow-up or in the 30 days after HHU discharge for, we found no associations between Charlson index >3 vs ≤3 (*P* = .587), or between antimicrobial drugs (*P* = .553), or between patients in whom *P. aeruginosa* was isolated and those in whom other pathogens or no pathogens were isolated (*P* = .440). However, patients aged >80 years were less likely to be readmitted to hospital OR = 0.5 (95%CI: 0.3-0.8) (*P* = .006) and patients with complications of AECOPD were more likely to be readmitted to hospital OR = 4.1 (95%CI: 2-8.7) (*P* < .0001). The multivariate analysis adjusted for type of antimicrobial drugs, Charlson index, age >80 years, Pseudomonas infection, and complication of AECOPD confirmed that complication of AECOPD was a risk factor for hospital readmissions and that age >80 years was not at major risk for hospital readmissions (Table 6).

TABLE 5 Univariate analysis of the effectiveness and safety of outpatient parenteral antibiotic therapy (OPAT) for acute exacerbation of chronic obstructive pulmonary disease

Variables	Effectiveness (*P*)	Safety (*P*)
Charlson index ≥3	.336	.522
Isolation *P. aeruginosa*	.593	.324
Self-dilution OPAT	.144	.193
Self-handling OPAT	.689	.417

4 | DISCUSSION

Outpatient parenteral antibiotic therapy has been under development all over the world for almost 4 decades. In countries such as the United States where health costs have a direct impact on patients and insurance companies, the outpatient approach has been more widely used than in Spain. In 2000, more than 250 000 patients in the United States underwent OPAT.[18]These data contrast with the relative paucity of research into the effectiveness and safety of OPAT for respiratory infections and especially with the lack of studies in this regard in patients with AECOPD.[19-21]

TABLE 6 Variables associated with hospital readmissions because of poor control of acute exacerbation of chronic obstructive pulmonary disease (univariate and logistic regression analyses)

	Univariate analysis		Logistic regression analysis*	
Variables	**OR (95%CI)**	***P***	**OR (95%CI)**	***P***
Antimicrobial therapy				
Carbapenem	1.3 (0.8-2.3)	.313	1.7 (0.8-3.9)	.199
Piperacillin/tazobactam	1.3 (0.8-2.2)	.318	1.5 (0.7-3.4)	.332
Cephalosporins	0.7 (0.4-1.2)	.250	0.9 (0.4-2)	.899
Quinolones	1 (0.5-2.3)	.909	1.7 (0.6-4.9)	.346
Charlson index >3	0.9 (0.5-1.4)	.587	0.9 (0.6-1.7)	.919
Age >80 years	0.5 (0.3-0.8)	.006	0.5 (0.3-0.9)	.017
P. aeruginosa infection	1.2 (0.7-2)	.440	0.8 (0.5-1.2)	.427
Poor control of AECOPD	4.1 (2-8.7)	<.0001	3.7 (1.6-8.3)	.002

*Statistical meaning ($P < .05$).
AECOPD, acute exacerbation of chronic obstructive pulmonary disease.

The European Respiratory Society consensus statement on COPD recommends managing moderate AECOPD patients at home and reserving hospital admissions for severe exacerbations.[22] Similarly, the Spanish COPD consensus statement[12] regards HHUs as an alternative for patients with AECOPD without respiratory acidosis. In a meta-analysis of 7 trials with a total of 754 patients, Ram et al[23] concluded that these alternatives to conventional hospitalisation are safe as long as patients are carefully selected, excluding those with mental disorders, radiological or electrocardiographic changes, significant comorbidities and low social support. In a more recent meta-analysis, Jeppensen et al[24] confirmed the effectiveness and safety of HHUs in patients with AECOPD.

Díaz Lobato et al[25] reported a study in Spain in AECOPD patients hospitalised in pneumology wards. Three days after admission, patients were randomised to continue treatment in the wards or to receive HHU care from a team consisting of a pneumologist and respiratory nurses. They found that HHU allows for recovery without increasing in readmissions, relapses or therapeutic failure. However, none of the hospitalised patients with AECOPD needed parenteral antimicrobial therapy. Despite the evidence and recommendations for the use of HHUs in AECOPD and other respiratory infections, this resource is relatively underused, as is also evidenced by the low number of pneumologists that actively participate in HHUs.

Few studies have analysed the effectiveness and safety of OPAT specifically on patients with AECOPD. Our results show that OPAT is effective and safe in patients with AECOPD, as 93.4% of the patients had favourable outcomes. Our study shows that the need for intravenous therapy in patients with AECOPD does not always require conventional hospitalisation. Nevertheless, 4 (1.1%) patients died at home; we consider this percentage acceptable, considering that our patients had severe COPD and high comorbidity. Technological advances have enabled different doses of medication to be safely administered in patients' homes, which is especially important in patients with severe COPD and repeated exacerbations, especially those caused by infection with *P. aeruginosa*, for which parenteral antibiotics are more often necessary and would otherwise require conventional hospitalisation.

Pseudomonas aeruginosa was the most frequent microorganism in our patients with AECOPD, being isolated in 38% of cases. Our study also confirms Garde et al[26] results in patients with respiratory infection caused by *P. aeruginosa*, some of whom had AECOPD as well as other conditions such as bronchiectasis, where OPAT supported by HHUs reduced hospital stays.

Antibiotics that cover Pseudomonas species are normally used in patients with severe acute exacerbation of COPD because this is the most frequently isolated microorganism. Some recommendations indicate that 7-day treatments are sufficient for Pseudomonas infection. However, in several other published guidelines, the recommended length of treatment for these antibiotics, nearly always administered parenterally, (except quinolones) is 10 days[27] All these patients met the indications for and underwent parenteral antibiotic therapy for at least 10 days. Occasionally, patients received two parenteral antibiotics, and the maximum length of treatment was 3 weeks. In our study, the mean stay (conventional hospitalisation + HHU) was 20.5 days. Although stay is not necessarily equivalent to the length of OPAT, 20.5 days clearly surpasses the recommendations for the length of treatment. Various explanations are possible: treatment may have been prolonged in some patients because of previous treatment failure or multiresistant pathogens.

Moreover, other microorganisms that are generally multiresistant in AECOPD, including methicillin-resistant *S. aureus* and extended spectrum beta-lactamase-producing gram-negative bacteria such as cephalosporin-resistant *K. pneumoniae* or *E. coli*, can also be treated by OPAT.[28] Regarding the isolation of microorganisms in the sputum culture in COPD, it is important to remember that 50% to 70% of cases of AECOPD are respiratory infections. Sputum analysis (Gram staining and cultures) is especially indicated to determine the type of microorganism in patients with severe, repeated exacerbations to ensure appropriate antibiotic coverage. However, it is not easy to obtain optimal cultures from all patients, so no microorganisms are isolated in about one-third of cases.[13] On the other hand, empirical antibiotic treatment is usually started in these patients before the results of sputum cultures become available. Antibiotic treatment

in AECOPD is recommended in patients with increased dyspnoea, fever, increased sputum volume or purulent sputum. Antibiotic treatment is also indicated in moderate-severe exacerbations requiring hospital admission, as in our study, because it reduces the incidence of pneumonia and mortality.[29]

We must highlight use of intravenous levofloxacin in 45 patients. The choice of the antibiotic was based on Spanish COPD guidelines (GesEPOC)[13] and depends on the knowledge of the bacterial species involved, the local antibiotic resistance, the severity of the exacerbation and the risk of *P. aeruginosa* infection. Among the recommended antibiotics is levofloxacin administered either orally or intravenously. It is usually recommended during the first days of treatment when respiratory deterioration is present, intravenous administration is recommended over oral administration. The pharmacokinetics of oral levofloxacin results in a high bioavailability (nearly equivalent to that of intravenous levofloxacin) and a long biological half-life. However, intravenous administration results in slightly higher concentrations, which, together with the avoidance of oral intake in the first days of respiratory exacerbation to prevent bronchoaspiration, can justify administering levofloxacin intravenously and would explain the cases in our study.

Patients with respiratory infections are rarely selected for OPAT. One of the few studies that analysed the effectiveness and safety of OPAT in respiratory infections included patients from respiratory day hospitals with community-acquired and nosocomial pneumonia, bronchiectasis and cystic fibrosis as well as patients with AECOPD. Moreover, as parenteral antimicrobial therapy was administered in the respiratory unit in the day hospital, conventional hospitalisation was avoided.[30] Our results are similar to those of this study, confirming that OPAT administered and controlled by admission to HHUs was safe and efficient.

Nearly all patients in our study were GOLD stages III and IV (predicted FEV1% was 38% ± 14, FEV1/FVC (%) 62% ± 13). Although not all patients had the FEV1/FVC ratios (<70%) required for the diagnosis of COPD, it is important to remember that in certain situations there is an associated restrictive pattern. The most frequent cause of an associated decrease in FVC is an obstruction to advanced airflow, as occurred in patients in this study. Another explanation for an associated restrictive pattern is a poor forced expiratory manoeuvre, especially in elderly patients. Other factors that can also cause an associated restrictive pattern and that are also associated with COPD include obesity (overlap syndrome), bronchiectasis and osteoporosis. Bronchiectasis in COPD is a consequence of recurrent respiratory infections. The usual functional pattern of bronchiectasis is airflow obstruction, but the progression of bronchiectasis to fibrosis also causes associated restrictive alterations.

Given that the highest cost of treating COPD is hospitalisation, it is important to develop strategies to manage AECOPD more efficiently and safely for frequently readmitted patients; OPAT with the support of HHUs is one such strategy. This strategy can avoid admissions to hospital from emergency rooms and can shorten and optimise ward stays by sending clinically stable patients to HHUs. In light of current budget restrictions, we also wanted to analyse whether using OPAT in patients with AECOPD resulted in financial savings. Hernandez et al[31] showed that using HHU in patients with AECOPD resulted in a 62% decrease in costs, essentially from shorter hospital stays. In our study, among the patients who spent time in conventional hospital wards prior to HHU, the mean stay was only 4.6 days, whereas the duration of the parenteral antimicrobial therapy in exacerbated COPD because of *P. aeruginosa* ranges between 10 and 14 days. Moreover, decreases in hospital stay were not related to increases in hospital readmissions.

The variable most often used to determine the effectiveness of OPAT is readmission to hospital. Only 5.5% visited the emergency room, despite the large percentage (48%) of patients with Charlson scores ≥3. Our results are similar to those reported by Pérez-Lopez et al,[32] who observed 7.5% unexpected returns and hospital readmissions among patients admitted to HHUs with different infections. The number of readmissions within 30 days of discharge from the HHU in our study was 15.7% lower than the 26% in the study reported by Allison et al,[33] although few patients in their study underwent OPAT for respiratory infections.

When we analysed the reasons for hospital readmission in our patients, we found that the main reason was poor control of AECOPD, and that age >80 years did not increase the risk of readmission. This finding is surprising, because most studies have found that older age is associated with a higher risk of hospital readmission in patients undergoing OPAT.[34] However, these results corroborate those recently published by our group[35] as well as by others,[36] providing evidence that OPAT can be safe and effective in elderly patients. Good outcomes in elderly patients might be partially explained by a lower incidence of nosocomial infections. These data reinforce our conclusion regarding the effectiveness and safety of OPAT in AECOPD, even in elderly patients.

We also analysed whether the participation of patients and/or caregivers in diluting medications and connecting and disconnecting the venous catheter posed an additional risk to effectiveness and safety. These aspects are particularly relevant in OPAT for conditions like AECOPD that often require parenteral administration more than once a day, where total reliance on administration by nursing staff requires many home visits. The complication rates for self-administration were not higher than for administration by the nursing staff, raising the possibility of decreasing the frequency of home visits by the nursing staff and thereby improving the efficiency of OPAT. To our knowledge, this is the first study to analyse the effectiveness and safety of self-administered OPAT in patients with AECOPD.

We observed no differences in the effectiveness or safety of OPAT in function of the pathogen isolated. The most frequently isolated pathogen was *P. aeruginosa*, which can cause serious complications, but patients infected with this pathogen did not have worse outcomes or require more visits to the emergency department than those in whom other pathogens or no pathogens were isolated.

Our study has limitations. It was a retrospective study, and the OPAT Registry from which our data were taken is not confined to respiratory infections. Thus, data about clinical conditions such as bronchiectasis, obesity, and osteoporosis, frequent comorbidities of COPD, were not available. Moreover, this retrospective study lacked a control

group. A control group of matched patients undergoing parenteral antibiotic therapy for AECOPD would have enabled direct comparisons of important variables and added strength to our conclusions; nonetheless, we were able to compare our results to those reported in other studies, and AECOPD patients receiving OPAT in conventional hospitalisation would logically have a longer mean hospital stays.

5 | CONCLUSION

We conclude that OPAT is effective and safe in appropriately selected patients with AECOPD admitted to HHUs. Considering that AECOPD patients with severe COPD and high comorbidity have a high risk of mortality and readmission to hospital, the results obtained in this study of effectiveness and safety seem optimal. Treating patients at home may be beneficial in terms of fewer complications. HHUs can help avoid or reduce hospital stays in patients with AECOPD who need parenteral antimicrobial therapy without increasing hospital readmissions and complications. However, more studies are required to confirm our findings.

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CONFLICTS OF INTEREST

Authors claim there is no conflict of interest. None of the listed authors have a financial interest. This study did not have any funding sources.

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