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Are treatment guides and rational drug use policies adequately exploited in combating respiratory system diseases?

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KEYWORDS
Asthma;
COPD;
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Pneumonia

Summary The aim of the present study was to increase awareness regarding the rational use of medicines. The data were obtained via the Material Resources Management System Module of the Ministry of Health. For the appropriateness of treatments, the Global Initiative for Asthma, the Global Initiative for Chronic Obstructive Lung Disease, and the guidelines for the rational use of medicines were used. We also investigated whether any de-escalation method or physical exercise was performed. Statistical analyses were performed using descriptive statistics to determine the mean, standard deviation, and frequency. The results showed that healthcare providers ignored potential drug reactions or adverse interactions, and

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reflecting the lack of adherence to the current treatment guides, 35.8% irrational use of medicines was recorded. Thus, de-escalation methods should be used to decrease costs or narrow the antibiotic spectrum, antibiotic selection should consider the resistance patterns, culturing methods should be analyzed, and monotherapy should be preferred over combination treatments.

Introduction

The World Health Organization (WHO) reported that chronic respiratory system diseases will increase in the future as a result of air pollution, global warming, and smoking [1]. In addition, chronic obstructive pulmonary disease (COPD) and pneumonia have been predicted as two of the leading causes of death [1,2]. In addition, the cost of the drugs and pharmaceutical products (DPP) used for the treatment of these diseases has been huge burden on government economies and social security administrations [3,4]. Studies have also reported that chronic diseases pose a threat to public health, and it might not always be possible to access effective treatments due to cost-related factors [5].

The aim of all healthcare providers is to effectively treat patients and avoid adverse reactions to medicine [6]. The aim of the present study was to reduce the economic cost of medical treatments via the implementation of policies regarding the rational use of drug. Despite the massive efforts of infection control committees, antibiotics have been irrationally consumed [7,8].

The present study included patients with COPD or pneumonia, diagnosed and admitted with chest diseases at a state hospital. The aim of the present study was to investigate the compliance of antibiotic use with laboratory, clinical, and recent guidelines and increase awareness regarding the rational use of drugs via the estimation of unit costs using pharmacoeconomic models, including cost-benefit-analysis (CBA) and cost-minimization analysis (CMA).

Materials and methods

Inclusion criteria

The study population included 1101 patients admitted to the Chest Diseases Service (30 beds) of Tekirdağ State Hospital (400 beds) between January 01, 2012 and December 31, 2012. For cost analyses, some patients were excluded for specific reasons.

According to the diagnosis, COPD, pneumonia, and asthma patients were included in the present study. Apart from this, intensive care unit patients, tuberculosis, bronchiectasis, pulmonary embolism, diffuse parenchymal lung disease and asthma, pneumonia with diabetes mellitus, congestive heart failure, chronic renal failure, sinusitis, and allergic rhinitis were excluded from the present study. Asthma and COPD, accompanied by pneumonia, were included in the group of pneumonia patients (Fig. 1).

The remaining cases ($n = 729$) were included in the study.

Data collection

The data were obtained from Material Resources Management System of the Ministry of Health. The system provided diagnosis, medical history, demographic features, and treatment data. As part of the treatment info, all DPP, including feeding solutions and serums with dose information, and culture antibiogram results for patients who used antibiotics were obtained and analyzed. Drug interactions commonly encountered in the patient records and the compatibility of these substances with the treatment guides and guidelines for the rational use of drugs were analyzed [9,10]. Moreover, whether physical exercise was recommended to reduce medicine costs was examined using random sampling in 10% of the population.

Cost evaluation

The cost of the drugs and pharmaceutical products was calculated using unit prices and the actual amount of medicine used. The unit prices were determined using the price list published by the Ministry of Finance and the Turkish Pharmaceutical and Medical Device Agency [11]. Following the calculation of the cost of antibiotics, another pharmacoeconomic analysis was performed using the CMA method, involving an alternative treatment method comparable but more economical than

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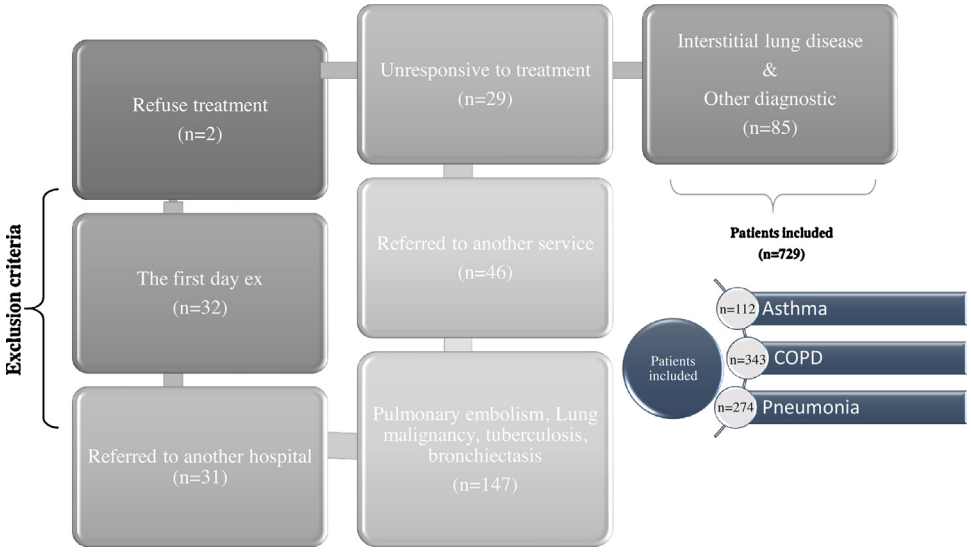

Figure 1 Inclusion and exclusion criteria.

that previously administered [12]. For the costs calculated in Turkish Liras (TL), the Euro (€) equivalent of TL of the period of expenditure was used for standardization (1 € = 1.9595 Turkish Liras).

Statistical evaluation

Descriptive analyses (mean, standard deviation, frequency) of the data obtained through a routine data recording system were made. To calculate the total pharmaceutical cost, the daily consumption of medicine was obtained after multiplying the box or unit price by the number of boxes or units. To calculate the mean total cost, the total cost was divided by the number of patients. The daily cost per patient was calculated by dividing the mean total cost by the mean hospital stay (days).

Ethics committee approval

The approval of the Tekirdag Province General Secretariat of State Hospitals Association was obtained on May 15, 2013, and the study was approved through the Local Ethics Committee of Namik Kemal University Faculty of Medicine on June 27, 2014, approval number 2013.70.06.01/01.

Results

The study included 729 patients (67.7% male; 32.3% female) diagnosed with asthma, COPD, or pneumonia. The mean ages of the male and female patients were 70.38 ± 0.50 and 69.09 ± 15.62 years old, respectively. The mean hospital stay of the patients was 21 days. The longest hospital stays were 41 days for COPD patients, 8 days for asthma patients, and 14 days for pneumonia patients. The total cost of inpatient DPP expenses of the hospital for the year in which the present study was conducted was €2,017,307.03. The total DPP cost of the participants of the present study for the same year was €373,497.45 (Table 1).

The mean total cost per patient was €512.34, and the mean daily cost per patient was €24.40. The mean total cost of antibiotic use was €350.80. The total DPP cost of the excluded patients was €234,187.70/year. The most popular antibiotics hospital-wide during the study period was ceftriaxone with 43,405 units costing a total of €220,846.06; however, among the study group, moxifloxacin was the most popular antibiotics with 3676 units consumed costing €104,154.90 (Fig. 2).

Quinolones were used the most in both study groups and throughout the entire hospital. The total cost of the antibiotic use of the study group was 19.05% of the total cost of antibiotic use at the hospital for the same time period (Fig. 3).

A total of 929 samples were collected from the study group: 529 sputum samples, 197 urine samples, 180 blood samples, and 23 endotracheal aspirate culture-antibiogram samples (Fig. 4).

Approximately 52.81% of the patients whose cultures showed no significant growth were prescribed a combination of moxifloxacin (400 mg/day) and ceftriaxone (2 g/day) for 8 days. In addition to moxifloxacin and ceftriaxone, ampicillin sulbactam (2 g/day) was administered to 7.13% of the participants ($n = 52$) for 10 days. Patients with *Streptococcus* ($n = 1$) were treated with ceftriaxone

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Table 1 The total DPP costs of the entire hospital, and patients with asthma, COPD, or pneumonia for the study period.

Pharmaceutical product	Study group cost (€)/year	Hospital cost (€)/year	Study group % (€)	Study group (%)
Antibiotics	255,730.99	1,342,784.18	19.05	13.55
Inhaled bronchodilators and steroids	54,837.64	170,749.17	32.12	24.52
Montelukast	142.98	436.74	32.73	32.74
Acetylcysteine	5723.49	32,488.51	17.62	22.77
Corticosteroids oral and IV	13,339.07	105,714.39	12.62	10.49
LMWH[a]	22,411.46	186,677.93	12.01	12.11
H_2 R.A.[b]	14,477.33	98,752.18	14.66	11.31
Allopurinol	21.61	89.67	24.11	11.44
PEFP[c]	6812.88	79,614.26	8.56	10.53
Total	373,497.45	2,017,307.03	18.52	16.98

[a] LMWH: low molecule weighted heparins.
[b] H_2 R.A.: H_2 receptor antagonists.
[c] PEFP: parenteral and enteral feeding products.

(2 g/day) and moxifloxacin (400 mg/day), although this pathogen is susceptible to penicillin, and no penicillin allergies were reported. In a COPD patient affected with the Enterobacteriaceae, although the culture antibiogram result showed susceptibility to amikacin, ciprofloxacin, and levofloxacin, the patient was empirically treated with ceftriaxone and moxifloxacin.

Approximately 11.65% of the patients ($n = 85$), with CRP and WBC values within the normal range and antibiogram results showing no significant growth, were treated with both ceftriaxone (2 g/day) and moxifloxacin (400 mg/day). Notably, 75% of the pathogenic bacteria in the culture materials ($n = 8$) were susceptible to levofloxacin; thus, moxifloxacin was prescribed costing €114.20 per patient.

Carbapenem and quinolone antibacterials were prescribed ($n = 10$), although the antibiogram results showed no need for antibacterials, which cost the hospital €1431.90. Due to methicillin-resistant *Staphylococcus aureus* (MRSA), this patient was switched to linezolid and cephoperazone-sulbactam. Similarly, empirically

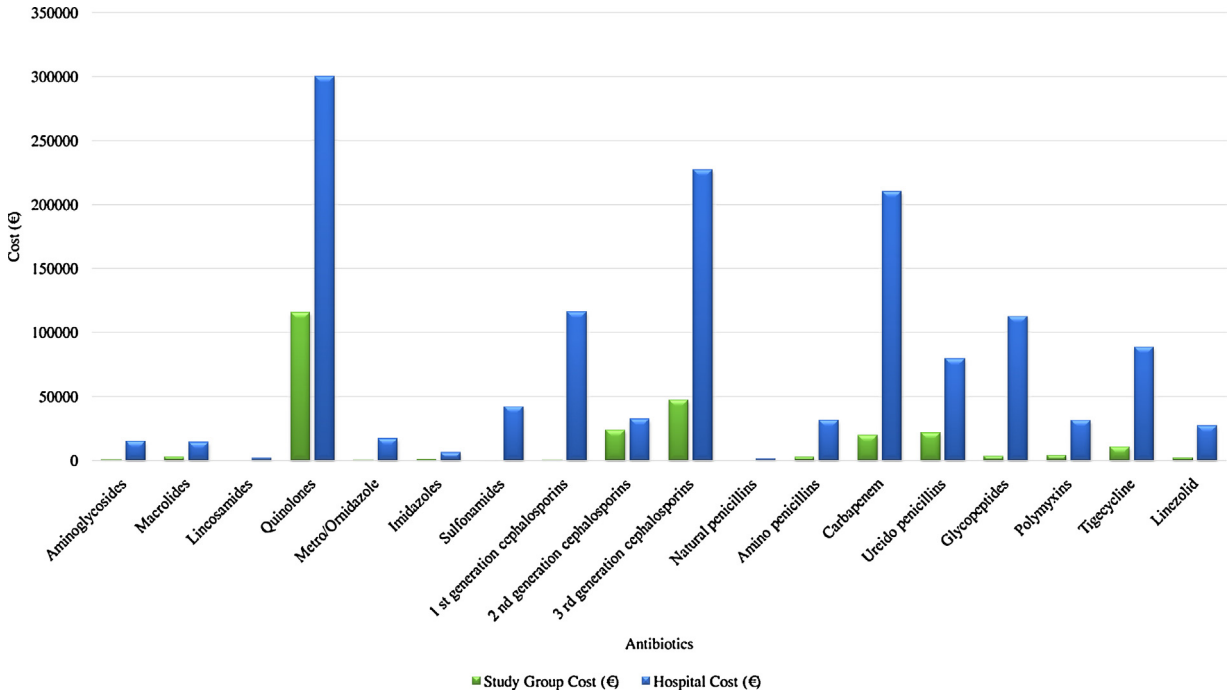

Figure 2 Antibiotics administered to the study group.

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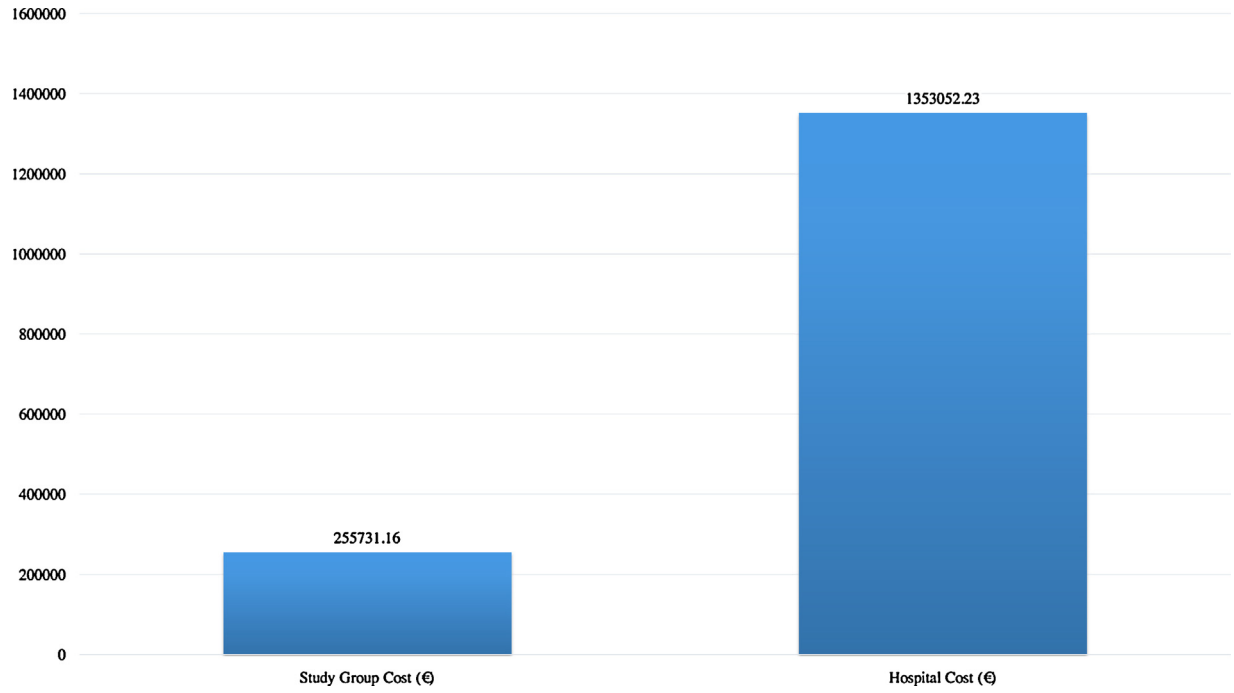

Figure 3 Comparison of the amount of antibiotics consumed by the study group and throughout the entire hospital (€).

treatments with ceftriaxone and moxifloxacin were switched to carbapenem and teicoplanin, although no culture growth was observed ($n = 6$). In 261 of the 729 patients (35.80%), based on culture antibiogram results and treatment guides, the irrational use of medicines was observed.

In patients diagnosed with asthma ($n = 112$), treatments not compatible with the Global Initiative for Asthma (GINA) guide were observed [9] (Table 2).

According to the GINA guidelines, antibiotics are not routinely recommended in asthma exacerbations. However for asthma occurrences not accompanied by infections, such as pneumonia and sinusitis, the patients were treated with antibiotics ($n = 112$).

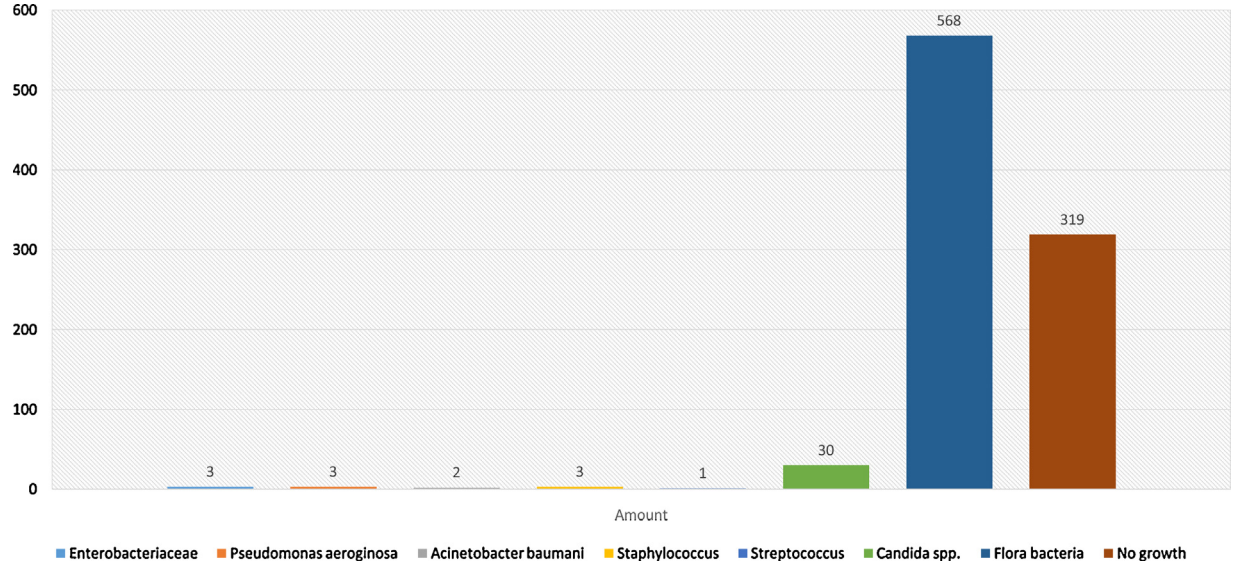

Figure 4 Results of the culture antibiogram obtained from the patients in the study group ($n = 929$).

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Table 2 Medication not suitable for asthma treatment.

Pharmaceutical product	Numeral	Cost (€)
Ampicillin sulbactam	249	359.62
Cefazolin	46	117.38
Cefuroxime	680	30,711.9
Ceftrixone	491	2498.22
Ciprofloxacin	44	604.26
Levofloxacin	59	122.55
Moksifloxacin tablet	198	448.65
Moksifloxacin vial	229	6488.43
Cefoperazone sulbactam	6	38.64
Piperacillin sulbactam	93	1100.15
Meropenem	11	132.03
Linezolid	18	1120.24
LMWH	194	926.69

Notably, 3770 units of acetylcysteine were used in various treatments for patients with bronchospasm ($n = 197$). Theophylline and other methylxanthines were used with allopurinol ($n = 6$) and/or fluoroquinolones ($n = 44$). In patients with respiratory tract infections ($n = 5$), montelukast was used. Pulmonary rehabilitation was not recommended to any of the patients.

Discussion

The estimation of unit drug costs, among the direct costs in healthcare services, is crucial. For hospitals, the treatment cost of respiratory system diseases, such as asthma, COPD, and pneumonia, are a large portion of the total hospital expenses [13]. The cost of treatments for respiratory diseases comprised 6% of the allocated total healthcare-related budget in EU. Majority of this cost (56%, 38.6 billion €) was COPD-related [14,15]. The direct cost of COPD in the US was estimated as 29.5 billion USD, with an additional estimated indirect cost of 20.4 billion USD [16]. Although, previous studies have investigated strategies to achieve the cost effective treatment of asthma [17], there are few pharmacoeconomic studies investigating the cost of drugs [18].

The aims of the present study aims was to investigate the cost of DPP for the treatment of patients admitted with asthma, COPD, and pneumonia and assess the compatibility of DPP use of the cohort with the current treatment guidelines.

In the literature, it has been reported that the mean hospital stay and cost per person for pneumonia patients were 4 days and 256.63 USD, respectively, and the Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2014 Guide recommends 5—10 days of antibiotic treatment for these patients [10,19,20]. In addition, antibiotic use in patients with COPD exacerbations might significantly reduce the duration of the hospital stay [21].

In the present study, the cost of antibiotics in patients with asthma, COPD, and pneumonia was 19.05% of the total cost of antibiotics used at the hospital during the same time period, and the cost of DPP and antibiotics per person was €512.34 and €350.80, respectively. The mean hospital stay was 21 days, and all patients were administered antibiotics. Compared with previous studies, the mean cost per person was higher in the present study, associated with a longer hospital stay.

Boucher et al. investigated the cost of DPP, occurrence of hospital infections, use of drug groups, and duration of hospital stay in 278 inpatients. These authors reported that DPP use for antimicrobial treatment, stress ulcer prophylaxis, and bronchodilator treatment comprised more than 66% of the total DPP use [22].

In the present study, the use of the same DPP was 79.92% of the total DPP use of the entire hospital and 87.03% for the study group, and these results were higher than the findings of Boucher et al. This difference might reflect the fact that the present study included patients with respiratory diseases, thus bronchodilator use was substantial. However, the difference between hospital-wide values might warrant an investigation of the drug use indications.

Previous studies have shown that the difficulty in differentiating infectious and non-infectious pathologies in pneumonia diagnosis might result in the irrational use of antibiotics, thereby leading to infections with bacteria resistant to antibiotic toxicity and an increase in the cost of treatment [23,24]. In COPD exacerbations, 50—70% of tracheobronchial infections (bacterial factors 40—50%, viral factors 30—40%, atypical bacterial factors 5—10%) and 10% of the air pollution were cited among the causes, but in 30% of the cases, no etiology was reported [25]. In addition to the difficulty in obtaining a differential diagnosis, amoxicillin, beta-lactam and beta-lactam inhibitors, second-generation cephalosporins, and macrolides were administered for mild exacerbations of COPD; third-generation cephalosporins or respiratory fluoroquinolones were administered for moderate exacerbations of COPD; and antipseudomonal antibiotics were administered for acute exacerbations of COPD and exacerbations with a risk of Pseudomonas, according to the Jindal for the COPD Guidelines Working Group [26].

The GOLD recommends clavulanic acid and/oraminopenicillin or tetracycline for the initial treatment of pneumonia. For hospitalized patients

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in general wards, the IDSA/ATS guidelines recommend antipneumococcal fluoroquinolone (e.g., levofloxacin, moxifloxacin) or the combination beta lactam plus macrolide [10,27].

Moreover, routine antibiotics therapy for asthma exacerbations is not recommended [12,15,28,29].

All patients participating in the present study were administered antibiotics, and the choice of antibiotics was primarily a combination of ceftriaxone and moxifloxacin, instead of monotherapy. Notably, the use of the combination of ceftriaxone and moxifloxacin instead of monotherapy resulted in overspending, totaling €36,801.74. In addition, the use of moxifloxacin flacon (€104,154.90, 3676 units/year) instead of levofloxacin flacon resulted in overspending, totaling €51,683.49. Further, despite the lack of any evidence of infection accompanying asthma, antibiotics in the amount of €43,742.07 were used.

A current treatment guide states that imipenem, meropenem, ertapenem, colymicin, vancomycin, teicoplanin, linezolid, and tigecycline should not be part of an empirical treatment, and antipseudomonal antibacterials, such as, ceftazidime, cefepime, cephoperazone sulbactam and piperacillin tazobactam, should be administered only in a risky group [19].

The eligibility of the antibiotics was evaluated according to antibiotic culture test results. Radiological, sputum, white blood cell count, fever, and C-reactive protein were also evaluated. In patients without infectious diseases, empirical treatment and antibiotics overuse were evaluated.

In the present study, however, there were indications of the use of these antibiotics in only five patients, and these drugs were irrationally used for other patients, resulting in overspending, totaling €71,947.75. In addition, MRSA patients were switched to linezolid and cephoperazone-sulbactam instead of treatment with linezolid. However, the reason for the addition of cephoperazone-sulbactam treatment was not understood.

A total of 52.81% of the patients with cultures showing no significant growth were administered moxifloxacin (400 mg/day) and ceftriaxone (2 g/day) for 8 days, costing the hospital €87,267.97 and €29,714.11, respectively. Additionally, in 7.13% of the patients, ampicillin sulbactam (2 g/day) was administered in addition to moxifloxacin (400 mg/day) and ceftriaxone (2 g/day), resulting in overspending, totaling €1502.02. In patients with cultures showing streptococcus, instead of penicillin costing only €39.20, ceftriaxone and moxifloxacin were administered, which cost the hospital €283.34.

Although the rate of identifying the active pathogen via culture growth in Turkey is between 21% and 44%, this rate was 1.7% in the present study. A study on culturing and increasing the rate of identifying the active pathogen would increase the effectiveness of such probes and facilitate the selection of the appropriate antibiotics and thereby reduce hospital costs. Considering the antibiogram results and the resistance patterns in 261 of the 729 patients (35.80%), the irrational use of antibiotics was clearly observed.

Previous studies have reported that the current and effective treatment might not always be accessible under financial restrictions, and thus, similar DPP with a lower cost might be selected [12,30,31]. However, maintaining the empiric antibiotic regimen until the end of the treatment has also been reported [30].

Low-molecular-weight heparins (LMWHs) are used in the treatment of venous thromboembolism, which frequently occurs among patients and is an avoidable cause of death [31—38]. For immobile, polysemic, and dehydrated COPD patients, prophylaxis is recommended. Moreover, in this guideline, the use of LMWH for infectious asthma exacerbations was considered appropriate [10,33]. Studies have shown that for each attempt to avoid deep vein thromboembolism, the use of LMWH resulted in $391 savings based on a pharmacoeconomic model, although the use of this drug was a large portion of the total DPP budget of the hospital [34,36].

In the present study, in COPD and pneumonia patients and asthma patients experiencing exacerbation, prophylactic LMWH was used, consistent with the literature. However, LMWH was administered to patients with no indication of infection, which increased the costs.

Although a systemic review claimed that in COPD patients, mucoactive agents reduce the frequency of exacerbations and decrease COPD-related disabilities, recent studies have shown that these effects and the positive effects on the quality of life are minimal [10,39]. Therefore, the routine administration of these drugs in COPD treatment is not recommended, but patients who experience tenacious sputum might benefit from mucolytics [10,38]. In addition, some studies have reported up to 48% severe bronchospasm resulting from acetylcysteine [39,40]. In the present study, acetylcysteine was administered to patients, resulting overspending, totaling €14,630.98.

In the present study, theophylline, which has a weaker bronchodilator efficacy compared with beta-agonist agents, might have been administered because this antibiotic does not cause tolerance in patients with bronchial asthma after long-term

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use. However, when administering theophylline, healthcare providers did not consider that theophylline interacts with several agents, and the effectiveness is reduced or toxicity is increased when used with several agents, such as antiarrhythmics, allopurinol, ciprofloxacin, and levofloxacin because the theophylline biotransformation is suppressed. Theophylline or other methylxanthines were administered to six patients using allopurinol and 44 patients using fluoroquinolones throughout the hospital stay without considering any drug interaction.

Montelukast, a leukotriene receptor antagonist, which can be used in addition to glucocorticoid and beta agonists in patients with mild and moderate asthma and in patients with asthma induced through exercise, cannot be used alone in chronic asthma treatment because this drug increases the risk of respiratory tract infection [40]. The GINA guide recommends montelukast in asthma treatment for stage 2 patients as an alternative to inhaled steroids [9]. For stage 3 and above asthma patients, inhaled steroids are recommended. However, antibiotic treatment is not recommended for asthma patients without pneumonia and sinusitis [9].

In the present study, montelukast was administered to five patients, which was not part of the treatment or prophylaxis of COPD. This irrational use of montelukast caused the overspending of hospital funds on DPP.

Pulmonary rehabilitation is an indirect factor decreasing the symptoms in COPD patients, increasing the quality of life, and enhancing the efficacy of the treatment, thereby decreasing the cost. Tsiachristas et al. investigated the changes in cost-effectiveness in 1322 patients treated in 16 different disease management plans. These authors observed that physical activity (21%) in COPD patients had a significant positive effect on cost-effectiveness [41].

Among the randomly selected data (10%), no pulmonary rehabilitation recommendation was observed; therefore, the cost-effectiveness analysis of the pulmonary rehabilitation and the cost-utility analysis of the increased quality of life were not conducted, which could be considered as a limitation of the present study.

The total DPP cost of the inpatients in the study period was €2,017,307.03, with €373,497.45 for asthma, COPD, and pneumonia patients for the same time period. The average total DPP cost per patient was €512.34, the average daily cost per patient was €24.40, and the average total cost of antibiotic therapy per person was €350.80. Moxifloxacin was the most popular antibiotic with a total annual cost of €104,154.90. All patients in the study group were initially administered antibiotics, and the choice of antibiotic treatment was primarily a combination of ceftriaxone and moxifloxacin instead of monotherapy, which cost the hospital €36,801.74, and the use of levofloxacin instead of moxifloxacin cost the hospital €52,471.41. It was a frequent practice to initiate empirical antibiotic treatment and complete the treatment using the same regimen; moreover, no de-escalation practice was observed to decrease the cost and narrow the antibiotic spectrum. Considering the results of the culture antibiograms and treatment guide recommendations, the irrational use of antibiotics was observed. Moreover, interactions among drugs were disregarded, and several occasions of drug use contradicting the treatment guides were observed. No pulmonary rehabilitation was recommended to the patients.

Conclusion

Based on the culture antibiogram results and related resistance patterns, the irrational use of antibiotics should be avoided. To this end, culturing methods should be re-evaluated, and the successful identification of active pathogens should increase the effectiveness of culturing and facilitate the selection of the appropriate antibiotic therapy, which would eventually decrease the DPP costs. Patient care should be approached from a multi-disciplinary point of view and evidence-based guidelines should be used. Teams should be established and led by experts of infectious diseases and pharmacology. In hospitals, pharmacoeconomic models and health economy policies should be urgently implemented.

Funding

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Competing interests

None declared.

Ethical approval

The approval of the Tekirdag Province General Secretariat of State Hospitals Association was obtained on May 15, 2013, and the study was approved through the Local Ethics Committee of Namik Kemal

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