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Clinical and economic analysis of antimicrobial therapy of chronic obstructive pulmonary disease exacerbations

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SUMMARY
The aim of the study was to analyse the clinical and economic indicators of the treatment of acute exacerbations of chronic obstructive pulmonary disease (COPD). The study focused specifically on antimicrobial therapy and the use of fluoroquinolones in the management of exacerbations.Data on the consumption of antibiotics to treat exacerbations in ambulatory care were derived from IMS Health. Also, an observational, retrospective analysis was carried out of patients who entered the clinical pathway for COPD exacerbations in University Hospitals Leuven.IMS Health data showed that there is a trend towards the increasing use of broad-spectrum penicillins and fluoroquinolones, and decreasing use of tetracyclines in the treatment of COPD exacerbations in ambulatory care in Belgium in the first half of the 2000s. The observational analysis enrolled 267 patients who were hospitalised between October 2000 and October 2005 to manage 359 exacerbations according to the clinical pathway. Median length of stay per exacerbation amounted to 10 days. Mean quality of life associated with an exacerbation was 74 using the Chronic Respiratory Disease Questionnaire. Median costs of hospital treatment amounted to €5514 (third-party payer reimbursement and patient co-payment) per exacerbation. Treatment costs were driven by hospital stay (75% of total costs), diagnostic and laboratory tests (20%) and medication (5%). Antibiotics played a role in the hospital management of 75% of exacerbations. Fluoroquinolones were used to treat more severe exacerbations. Treatment of acute exacerbations of COPD imposes a significant clinical and economic burden on patients, the healthcare system and the society.

What's known
- Little is known about the use of antibiotics and their impact in treating COPD exacerbations.
- Few data are available about the costs of treating COPD exacerbations in hospital.

What's new
- Broad-spectrum penicillins and fluoroquinolones are increasingly used to treat exacerbations in ambulatory care.
- Costs of treating exacerbations in hospital are considerable and are primarily driven by costs of hospital stay.
- Fluoroquinolones are used to treat more severe exacerbations in hospital.

Introduction

Chronic obstructive pulmonary disease (COPD) is a disease typified by chronic airflow limitation which is not fully reversible. The airflow limitation tends to be progressive and is linked with an abnormal inflammatory response of the lungs to noxious stimuli (1). Acute exacerbations of COPD are generally defined by the presence of one or more of the following clinical symptoms: increase in sputum purulence, increase in sputum volume and worsening of dyspnoea (2). Exacerbations occur more frequently and increase in severity in patients with more severe underlying COPD (3). COPD patients tend to have 1–3 exacerbations per year (4).

Treatment of COPD exacerbations may require hospitalisation and is associated with significant mortality, morbidity, compromised quality of life and healthcare costs. Nearly 620,000 patients with an exacerbation were hospitalised in the USA in 2002, making exacerbations as one of the top 10 causes of hospitalisation among adults (5). Ten per cent of all acute hospital admissions are attributed to exacerbations in the UK (6). Mortality of hospitalised patients with exacerbations is approximately 10% and increases with the severity of exacerbation (4). Fifty per cent of hospitalised patients require re-admission to hospital at least once in the next 6 months (7). The cost-of-illness literature shows that inpatient costs represent the principal component of costs of treating exacerbations, accounting for 44–97% of direct healthcare costs (8).

Limited data are available about the management of hospitalised patients with COPD exacerbations. Guidelines on the diagnosis, management and prevention of COPD issued by the World Health Organization Global Initiative for Chronic Obstructive Lung Disease recommend oral or intravenous glucocorticosteroids in addition to bronchodilator therapy in the hospital management of acute

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exacerbations of COPD (1). Antimicrobial therapy is effective when patients with worsening dyspnoea and cough also have increased sputum volume and purulence. The choice of antibiotic has implications for drug acquisition costs, hospitalisation costs, time to resolution of symptoms, treatment failure and time between exacerbation episodes (8).

The aim of this study is to provide a clinical and economic analysis of treatment of acute exacerbations of COPD, with a particular focus on antimicrobial therapy. First, data are presented on the consumption patterns of antibiotics used to treat exacerbations in ambulatory care in Belgium. Second, an observational, retrospective analysis was carried out of patients who entered the clinical pathway for COPD exacerbations in University Hospitals Leuven. This analysis measures clinical and economic indicators of hospital management of exacerbations according to the clinical pathway, documents patterns of antimicrobial therapy of exacerbations, and investigates the relation between choice of antibiotic and treatment indicators. This information may be useful to physicians treating patients suffering from acute exacerbations of COPD.

Methods

Treatment of exacerbations in ambulatory care

Data on antimicrobial therapy in ambulatory care in Belgium were derived from IMS Health. These data referred to the indication of COPD. However, as the use of antibiotics has a role to play in the management of COPD exacerbations, but is not recommended in the treatment of stable COPD (1), it was assumed that antimicrobial data related to COPD exacerbations. IMS Health data were based on the prescriptions issued by a panel of 500 physicians. This concerns antimicrobial prescriptions to patients seen by physicians of all specialities offering general medical services, except for hospital inpatients. The composition of the panel of physicians corresponds to the distribution of the Belgian population of physicians by speciality and by region. When extrapolating the number of antimicrobial prescriptions issued by the panel of 500 physicians to the Belgian population, care was taken that the frequency of results adheres to the Gauss curve as closely as possible.

Treatment of exacerbations in University Hospitals Leuven

Patients

Patients were admitted to the Respiratory Division of University Hospitals Leuven, a 1900-bed university teaching hospital, between October 2000 and October 2005. Patients were enrolled in the study if they suffered from an acute exacerbation of COPD as defined by an increase in sputum purulence, increase in sputum volume and worsening of dyspnoea. Diagnosis of an infectious exacerbation was based on the presence of fever, increase in C-reactive protein levels and the results of sputum culture. As this study consisted of a retrospective analysis of anonymous medical records and patient invoices, ethical approval was not needed.

Clinical pathway

Patients entered the clinical pathway for COPD exacerbation used in the University Hospitals Leuven. The clinical pathway is a standard treatment pathway that informs bronchodilator and ant-inflammatory therapy. It does not offer guidance on the choice of antimicrobial therapy. The pathway, however, does advice the use of antibiotics in general only if signs of infection are present: clinical signs such as fever and purulent sputa, biochemical signs such as C-reactive protein and leucocytosis, radiological signs such as infiltrates. Local microbiology guidance is provided in few patients, in essence those patients who do not respond well to the initial therapy.

According to this clinical pathway, patients are hospitalised for 8 days (10 days until May 2003), during which time they receive standardised medication and care. In the 8-day clinical pathway, patients received oral methylprednisolone 32 mg/day for 4 days followed by 32 or 24 mg/day for 4 days. Additionally, short-acting bronchodilators were prescribed four times a day for 3 days, three times a day for 4 days and two times a day for 1 day. In the 10-day clinical pathway, oral methylprednisolone was administered in a doses of 32 mg/day during 7 days and 24 mg/day during the following 3 days. Patients received the short-acting bronchodilators four times a day for 3 days, three times a day for 4 days and two times a day for 3 days.

Clinical and economic indicators

Demographic and clinical variables were gathered from medical records. Demographic characteristics were age, gender, height and weight. At patient level, the study calculated the mortality rate and the annual frequency of COPD exacerbations treated in hospital. The latter was computed by dividing the number of exacerbations by the number of days that patients participated in the study, and multiplying by 365. At exacerbation level, data were collected on the forced expiratory volume in 1 s (FEV_1) % predicted at admission to hospital. Also, the length of hospital stay for an exacerbation was reported. Finally, a

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disease-specific health-status measure, the Chronic Respiratory Disease Questionnaire (CRDQ), was used to assess the quality of life (9). This instrument has been found to provide a valid and responsive measure of quality of life associated with COPD exacerbations (10). The CRDQ consists of four dimensions: dyspnoea (Likert-score of 5–35), fatigue (score of 4–28), emotional function (score of 7–49) and mastery (score of 4–28). A higher total score indicates better health-related quality of life. A 2-week recall period was employed for the measurement of quality of life.

Cost data were derived from patient invoices. The economic analysis calculated direct healthcare costs associated with the treatment of a COPD exacerbation in hospital. Direct healthcare costs included medication costs, costs of hospital stay, and costs of diagnostic and laboratory tests. Costs were measured from a societal perspective, covering both patient co-payment and reimbursement by the Belgian third-party payer. Costs of transportation from/to the hospital and productivity losses were not taken into account. Costs were expressed in 2005 values.

Statistical analysis

The Kolmogorov–Smirnov test was applied to test for normality of continuous variables. Data were reported as number of patients (%) for binary and categorical variables, as means ± standard deviation for normally-distributed continuous variables or as median (range) for not-normally distributed continuous variables. The relation between choice of antibiotic and clinical/economic indicators was examined by means of the independent samples *t*-test or Mann–Whitney *U*-test depending on the normality of variables. CRDQ dimensions were recoded on a scale of 1–7 and differences between rescaled dimensions were tested by means of ANOVA. A p-value of 0.05 was used for statistical significance. Data were analysed in spss 14.0 for Windows (SPSS; Chicago, IL, USA).

Results

Treatment of exacerbations in ambulatory care

Figure 1 presents the volume of consumption of the various antimicrobial classes that are used in treating acute COPD exacerbations in ambulatory care in Belgium. Volume of consumption rose from 3.19 defined daily doses per 1000 inhabitants daily (DID) in 2001 to 3.86 DIDs in 2005. Shifts appear to have occurred in antimicrobial classes used to treat exacerbations. Volume of tetracyclines fell from 0.77 DIDs in 2001 to 0.39 DIDs in 2005. Conversely, increases were observed in the volume of broad-spectrum penicillins from 0.92 DIDs in 2001 to 1.55 DIDs in 2005 and in the volume of fluoroquinolones from 0.17 to 0.39 DIDs. The use of antibiotics in the treatment of COPD exacerbations was associated with substantial expenditure: consumption valued at public prices was €35,282,110 in 2005. This corresponds with 21% of expenditure on antibiotics in ambulatory care in Belgium during the same time period.

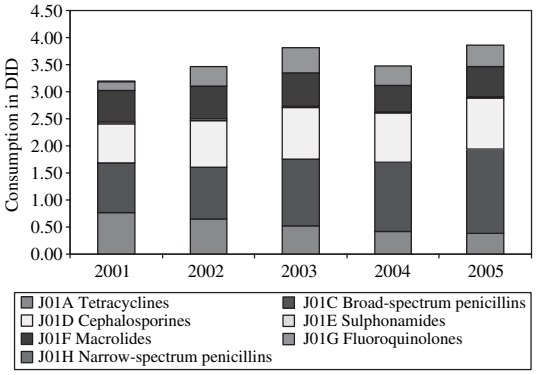

Figure 1 Belgian antimicrobial consumption for exacerbations in ambulatory care

Treatment of exacerbations in University Hospitals Leuven

Two hundred and sixty-seven patients hospitalised with an acute exacerbation of COPD were enrolled in our study. Their demographic characteristics are presented in Table 1. The majority of patients were aged over 60 years, with a mean age of 70 years (38–92 years). Patients were predominantly male

Table 1 Demographic characteristics of patients (n = 267)

Characteristics	Data
Age	
<40 years	1 (0.4%)
40–49 years	5 (2%)
50–59 years	30 (11%)
60–69 years	88 (33%)
70–79 years	111 (42%)
80–89 years	31 (12%)
≥90 years	1 (0.4%)
Gender	
Men	203 (76%)
Women	64 (24%)
Height (cm)	167 ± 9
Weight (kg)	68 ± 15

Data are expressed as the number of patients (%) or as means ± standard deviation.

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Table 2 Clinical and economic indicators of treatment

Indicator	Findings	Number of exacerbations
FEV_1 % predicted at admission	34% (12–91%)	316
Length of stay	10 days (3–55 days)	359
Quality of life (CRDQ)		
Dyspnoea	15 ± 6	33
Fatigue	14 ± 5	
Emotional function	28 ± 9	
Mastery	17 ± 6	
Total	74 ± 21	
Costs		
Medication	€244 (€9–4593)	359
Hospital stay	€4069 (€904–24,412)	
Diagnostic and laboratory tests	€1074 (€392–4601)	
Total costs	€5514 (€1486–31,285)	

Data are expressed as means ± standard deviation for normally distributed variables and as median (range) for not-normally distributed variables. CRDQ, Chronic Respiratory Disease Questionnaire; FEV_1, forced expiratory volume in 1 s.

(76%). The sample had a mean height of 167 cm and weight of 68 kg. Sixty-nine out of 267 patients were confirmed to have died during the study period, keeping in mind that the status could not be determined of 25 patients that the hospital lost contact with.

Patients suffered from 522 COPD exacerbations between October 2000 and October 2005, generating a median annual frequency of COPD exacerbations treated in hospital of 0.40 (0.20–4.15) per patient. Of these exacerbations, 359 exacerbations were treated according to the clinical pathway, while 163 exacerbations were not. No data on clinical and economic indicators of treatment were available for the latter.

Table 2 outlines the clinical and economic indicators of hospital treatment of COPD exacerbations according to the clinical pathway. At hospital admission, exacerbations had a median value of FEV_1 34% predicted. Median length of stay amounted to 10 days per exacerbation. Data on health-related quality of life were available for 33 exacerbations only. These data indicate that quality of life associated with a COPD exacerbation treated in hospital was impaired: the mean total quality of life score was 74 on a scale of 20–140. Lower scores were observed on the dyspnoea dimension than on the emotional function ($p = 0.007$) and mastery ($p = 0.001$) dimensions. Economic indicators focused on the costs of hospital treatment for a COPD exacerbation. Median total costs amounted to €5514 per exacerbation. The drivers of total treatment costs were – in descending order of importance – hospital stay (75% of total costs), diagnostic and laboratory tests (20%) and medication (5%). Costs of antimicrobial therapy made up 23% of medication costs.

Focusing on antimicrobial therapy, no antibiotic was used in 88 exacerbations (25%), an antibiotic belonging to a single antimicrobial class was administered to manage 198 exacerbations (55%), and antibiotics belonging to multiple classes were used to treat 73 exacerbations (20%). Treatment with a single antimicrobial class took the form of penicillins

Table 3 Association between fluoroquinole use and treatment indicators

Indicator	Treatment with fluoroquinolone	Treatment with other antibiotic	p-value*
FEV_1 % predicted at admission	28% (13–81%)	34% (12–91%)	0.042
Length of stay	11 days (4–40 days)	10 days (3–55 days)	0.327
Costs of medication	€323 (€71–4593)	€267 (€36–3360)	0.086
Costs of hospital stay	€4521 (€1356–17,631)	€4069 (€904–24,412)	0.303
Costs of diagnostic and laboratory tests	€1097 (€470–3551)	€1085 (€403–4601)	0.018
Total costs	€5979 (€1906–22,197)	€5616 (€1486–31,285)	0.330

Data are expressed as median (range). *Mann–Whitney U-test. FEV_1, forced expiratory volume in 1 s.

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(113 exacerbations, 57%), cephalosporins (50 exacerbations, 25%) and fluoroquinolones (34 exacerbations, 17%), but no tetracyclines, macrolides or sulfamides were administered. Thirty-four per cent of therapies drawing on multiple antimicrobial classes involved a fluoroquinolone, generally in conjunction with a penicillin. These data show that fluoroquinolones were used in the management of 59 out of 359 COPD exacerbations (16%).

Finally, the association between the use of fluoroquinolones and clinical/economic indicators was explored (see Table 3). Treatment costs with fluoroquinolones exceeded those with other antibiotics, but this was only statistically significant for costs of diagnostic and laboratory tests. Higher costs may originate from the fact that fluoroquinolones were used to treat more severe COPD exacerbations: the median value of FEV_1 % predicted at admission was 28% with fluoroquinolones as compared with 34% with antibiotics other than fluoroquinolones. No significant differences were observed between treatment with fluoroquinolones or with other antibiotics in terms of length of stay.

Discussion

This study carried out a clinical and economic analysis of treatment of acute exacerbations of COPD. The study focused specifically on antimicrobial therapy and the use of fluoroquinolones in the management of exacerbations.

Belgian data on the use of antibiotics in the treatment of exacerbations in ambulatory care point to an increase in volume from 2001 to 2005 and a shift in consumption patterns away from tetracyclines towards broad-spectrum penicillins and fluoroquinolones. The shift in antimicrobial prescribing patterns may reflect, amongst other things, local patterns of resistance in Belgium. For instance, data from the Belgian Pneumococcal Reference Laboratory indicate that resistance of *Streptococcus pneumoniae* increased from 16.4% in 1986 to 30.2% in 2003 in the case of tetracyclines. Conversely, resistance to penicillins was 13% in 2003. Also, a recent study found limited resistance of *S. pneumoniae* to fluoroquinolones: below 1% for levofloxacin and 0% for moxifloxacin in 2004 (11).

An observational, retrospective analysis was also carried out of patients who entered the clinical pathway for COPD exacerbations in University Hospitals Leuven. Few studies have measured health-related quality of life during acute exacerbation of COPD (12). Our study made use of the CRDQ. This instrument is suitable for use during exacerbations as it measures both the physical and emotional aspects of chronic respiratory disease. Quality of life associated with a COPD exacerbation treated in hospital was impaired, particularly with respect to dyspnoea. This is a significant finding as dyspnoea is considered to be one of the most distressing and disabling symptoms of chronic respiratory disease (13).

Direct healthcare costs associated with the treatment of COPD exacerbations in University Hospitals Leuven were substantial. This is because our sample of patients tended to suffer from severe exacerbations with a median value of FEV_1 34% predicted at admission. Exacerbation severity is an important determinant of direct healthcare costs, as studies have shown that costs increase with the severity of the exacerbation (14,15). Moreover, patients stayed in hospital for a median duration of 10 days per exacerbation, with costs of hospital stay accounting for 75% of direct healthcare costs. The observed median length of stay of 10 days is in line with results reported in the international literature (16,17). Our findings showed that medication costs are limited: they made up 5% of total hospital treatment costs. Similarly, a retrospective analysis of a nationwide sample of US inpatients found that 11% of hospital costs could be attributed to medication (18). The relative importance of hospital stay and medication in driving treatment costs suggests that larger savings could be attained by decreasing hospital length of stay rather than by reducing medication costs. Indeed, modifications and other modes of delivery in COPD exacerbations have been described that may result in substantial savings. These include assisted discharge (19,20), home care and teleconsulting (21).

Antibiotics were prescribed in the hospital management of 75% of exacerbations. Although there is some controversy over the role of bacterial infections, literature reviews and meta-analyses have found that antibiotics improve clinical indicators in COPD exacerbations and that patients with more severe exacerbations benefit more from antibiotics (22–24). Studies suggest that fluoroquinolones are marginally more or equally effective as first-generation antibiotics (e.g. aminopenicillins, macrolides and tetracyclines) (25,26). However, this literature is limited by the fact that most trials are powered to demonstrate equivalence rather than clinical superiority; have enrolled small samples that are not always representative of the patient population; and do not control for concomitant therapy or for comorbidities. Sixteen per cent of exacerbations in our study were treated with a fluoroquinolone. Their use appeared to be associated with the severity of the exacerbation: fluoroquinolones tended to be prescribed in the management of more severe exacerbations. Other factors that play a role in the choice of

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antibiotic in the Respiratory Division of the University Hospitals Leuven are local patterns of microbial resistance, costs, effectiveness, dose form, ease of administration, frequency of dosing, spectrum of activity, duration of treatment, adverse effect profile and potential drug interactions.

A recent literature review has found that fluoroquinolones may have a favourable economic profile as compared with first-generation antibiotics (8). This seems to arise from the fact that fluoroquinolones have higher acquisition costs, but are also associated with less treatment failure, more time between exacerbation episodes and lower hospitalisation costs. This points to a potential role for fluoroquinolones as a first-line treatment for COPD exacerbations in the presence of increased resistance to first-generation antibiotics or for patients who are at increased risk of treatment failure. The Canadian Thoracic Society and the Canadian Infectious Disease Society recommend fluoroquinolones as first-line treatment for patients suffering from chronic bronchitis (CB) exacerbations who are at the risk of failing therapy with first-generation antibiotics such as aminopenicillins, macrolides and tetracyclines (27).

The findings must be interpreted with the following caveats in mind. To the extent that antibiotics are used in the management of stable COPD, IMS Health data may overestimate the use of antibiotics to treat COPD exacerbations in ambulatory care in Belgium. Our findings relate to exacerbations treated according to the clinical pathway used in University Hospitals Leuven. If a patient did not respond well to the pathway treatment and was re-admitted, a tailored approach to treating the exacerbation was chosen. As those exacerbations did not follow the standard examinations and treatment planned by the pathway, clinical and economic indicators were not registered in our database. This specific group of exacerbations would warrant a separate data collection and investigation. Our analysis was not able to monitor progression of an exacerbation during the treatment course because of missing data on FEV_1 values. Finally, the data on unit costs were based on official reimbursement tariffs and patient co-payments applicable in Belgium, and healthcare resource use reflects clinical practice in University Hospitals Leuven. Therefore, our estimates of hospital costs of COPD exacerbations may not be generalisable to other institutions or countries.

Conclusions

In summary, there is a trend towards increasing use of broad-spectrum penicillins and fluoroquinolones, and decreasing use of tetracyclines and macrolides in the treatment of acute exacerbations of COPD in ambulatory care in Belgium in the early 2000s. This study has also shown that antibiotics play a role in the majority of exacerbations managed according to the clinical pathway used in University Hospitals Leuven. Quality of life associated with an exacerbation treated in hospital was impaired. Inpatient costs associated with the management of acute exacerbations of COPD were substantial and were primarily driven by the costs of hospital stay.

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