CLINICAL

A. Trippetti

COPD COMPLICATED BY BRONCHIECTASIS – OBSERVATIONAL STUDY

SUMMARY

COPD complicated by Bronchiectasis is one of the chronic degenerative pathologies that has always involved the General Practitioner in dealing with its frequent exacerbations during the cold season, despite the administration of influenza vaccination, pneumococcal vaccination, bronchodilators (steroids, inhalers and not, long acting beta-2-agonists, and antimuscarinics) as prescribed according to the GOLD guidelines.
– This observational study has been conducted for 5 consecutive years on 12 patients aged between 54 and 99 years. All patients have been treated according to the GOLD guidelines; a Group of 6 was also given, from October to May of each year, BrSM and PRM medicines for the prophylaxis of the seasonal colds.
The aim of this study was to detect whether there is a significant difference between the 2 Groups in relation to the recovery from the disease, assessing indicators such as:
1) home/medical clinic on-demand visits, 2) sick days, 3) use of antibiotics, 4) use of steroids and/or other drugs.
To demonstrate if the preventive overlapping therapy (conventional + BrSM and PRM therapies) is a feasible strategy for General Medicine, it is important: 1) to reduce the prescriptions of antibiotics (resistances), 2) to comply with the programmed spending limits (prescription appropriateness), 3) to comply with the state law (spending review), and, last but not least, 4) to improve the patient's well-being.

KEY WORDS

COPD, BRONCHIECTASIS, SPIROMETRY, CITOMIX, GUNA-FLU, GUNA-ANTI IL 1, GUNA-INTERLEUKIN 10, ECHINACEA COMPOSITUM S, UBICHINON COMPOSITUM, COENZYME COMPOSITUM®

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INTRODUCTION

COPD (Chronic Obstructive Pulmonary Disease) is a major public health problem and one of the leading causes of mortality (Lozano *et* Al., 2012) and chronic morbidity the world over.

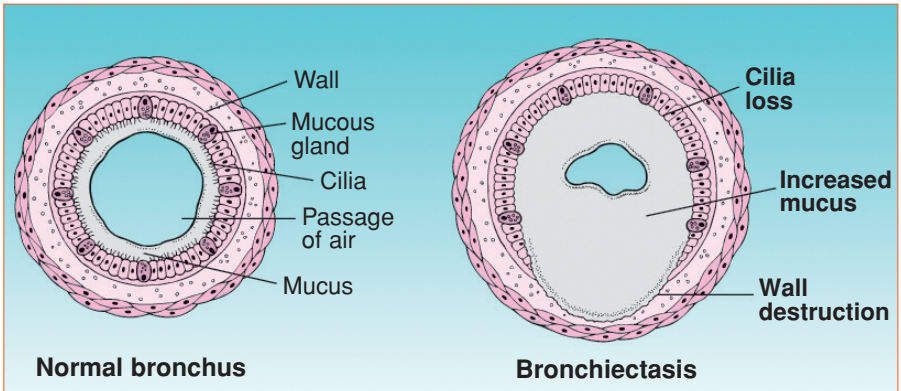
– Over the next few decades, it is anticipated that COPD will be the third cause of death worldwide, after cardiovascular disease and cancer, and that its social cost will increase as a result of continuous exposure to risk factors and the ageing of the population (Mathers *and* Loncar, 2006).

THE DISEASE

COPD is a disease characterised by persistent breathing difficulties and limitation of the airflow in the small airways (obliterative bronchiolitis) and subsequent parenchymal involvement, with rupture of the interalveolar septa resulting in the formation of air bubbles (emphysema) that reduce the capacity for gas exchange between the pulmonary capillary blood and inhaled air, with consequent initial and progressive hypoxaemic and/or hypercapnic respiratory failure.

– Bronchiectases are chronic dilations of the bronchii with a calibre greater than 2 mm due to the destruction of their walls (FIG. 1).
Bronchiectasis can be congenital or acquired, due to illness, such as chronic bronchitis, inflammation, or other factors.
The most common initial symptoms include **dyspnoea**, **cough** and/or **production** of **sputum**.
These symptoms are often underestimated by patients.

Although the main risk factor for COPD is inhaled cigarette smoke, environmental exposure, such as biofuel vapours and atmospheric pollution, can also be a causal factor (Paulin *et* Al., 2015).



Bronchiectases are chronic dilations of the bronchii, with a calibre greater than 2 mm, due to the destruction of their walls.

FIG. 1

– In addition to environmental exposure, there are also a number of host-related factors that make an individual more susceptible to the development of COPD, including: **1)** genetic abnormalities; **2)** abnormal lung development (Stoller *and* Aboussouan, 2005), and **3)** premature ageing.

COPD can be characterised by acute periods in which there is a considerable deterioration in the respiratory symptoms.
In most patients, COPD is associated with significant chronic diseases that increase its morbidity and mortality.

DIAGNOSIS

A clinical diagnosis of COPD should be considered in all patients experiencing dyspnoea, chronic cough, sputum production and/or a history of exposure to the risk factors for the disease.

Collection of a detailed medical history is fundamental in the case of confirmed or suspected COPD (TAB. 1).

Spirometry is essential for clinical diagnosis in this setting (Buist *et* Al., 2007); the presence of a post-bronchodilator FEV1/FVC ratio **<0.70** confirms the presence of a persistent bronchial obstruction and – consequently – COPD in patients with appropriate symptoms and considerable exposure to harmful stimuli.

– Spirometry is the most reproducible and objective measurement of airflow limitation and a readily available and non-invasive technique.

Despite its good sensitivity, the measurement of peak exhalatory flow alone cannot be reliably used as the sole diagnostic test, due to its poor specificity (Jackson *and* Hubbard, 2003).

DIFFERENTIAL DIAGNOSIS

The main differential diagnosis is with asthma.

– In certain patients with chronic asthma, it is not possible to make a clear distinction from COPD using the imaging techniques and functional tests currently available.
In patients with COPD, treatment is similar to that for asthma.
Other potential diagnoses are usually easier to distinguish from COPD (TAB. 2).

Alpha-1 antitrypsin deficiency (AATD) screening.

TAB. 1
Key indicators for the diagnosis of COPD.

A diagnosis of COPD should be considered and spirometry performed if any of the following indicators are present in an individual over 40 years of age. – These indicators are not diagnostic per se; the presence of multiple indicators increases the likelihood of a diagnosis of COPD. Spirometry is required to confirm the diagnosis of COPD.	
Dyspnoea	Worsens over time Usually gets worse with physical exertion Persistent
Chronic cough	May be intermittent and/or non-productive Recurrent wheezing
Chronic sputum production	Any type of chronic sputum production can indicate the presence of COPD
Recurrent lower respiratory tract infections	
History of exposure to risk factors	Host factors Tobacco smoke Smoke from biofuels used for home cooking and heating fuels Occupational dusts, vapours, fumes, gases and other chemicals
Family history of COPD and/or childhood factors	Low birth weight, childhood respiratory infections

COPD	Onset in mid-life Symptoms slowly progressive History of tobacco smoking or exposure to other types of smoke
Asthma	Onset early in life (often childhood) Symptoms vary widely from day to day Symptoms worse at night/early morning Allergy, rhinitis and/or eczema also present Family history of asthma Obesity coexistence
Congestive heart failure	Chest x-ray shows dilated heart, pulmonary oedema. Pulmonary function tests indicate volume restriction, not airflow
Bronchiectasis	Large volumes of purulent sputum Commonly associated with bacterial infection Chest x-ray/CT shows bronchial dilation, bronchial wall thickening
Tuberculosis	Onset all ages Chest x-ray shows lung infiltrate Microbiological confirmation High local prevalence of tuberculosis
Obliterative bronchiolitis	Onset at younger age, non-smokers May have history of rheumatoid arthritis or acute fume exposure Seen after lung or bone marrow transplantation
Diffuse panbronchiolitis	Primarily seen in patients of Asian descent Most patients are male and non-smokers Almost all have chronic sinusitis Chest x-ray and HRCT show diffuse, small, centrilobular nodular opacities and hyperinflation

These factors tend to be characteristic of the respective diseases, but are not mandatory. For example, a person who has never smoked may develop COPD (especially in the developing world, where other risk factors may be more important than smoking); asthma may develop in adult and even in elderly patients.

TAB. 2

COPD – Differential diagnosis.

The World Health Organisation recommends that all patients with a diagnosis of COPD should be screened for this condition at least once, especially in areas with a high prevalence of Alpha-1-antitrypsin deficiency (WHO Meeting Participants, 1997).

– A low concentration (<20%) is highly suggestive of homozygous deficiency.

Family members should also be screened.

CLASSIFICATION OF OBSTRUCTION SEVERITY

The classification of airflow limitation severity used in COPD is shown in TAB. 3. Specific spirometric cut-points are used for purposes of simplicity.

Spirometry should be performed after the administration of an adequate dose of at least one short-acting inhaled bronchodilator in order to minimise variability.

– It should be noted that there is only a weak correlation between FEV1, symptoms and impairment of a patient's health status.

For this reason, formal symptomatic assessment is also required.

STUDY DESIGN

This clinical study is based on the observation of COPD patients subject to frequent exacerbations, often with 3-4 or more episodes in the same winter, especially when living in large families or with children, who are particularly susceptible to seasonal viral illnesses.

– In these conditions, it is not possible to adopt the strategies indicated in the GOLD (Global Initiative for Chronic Obstructive Lung Disease) Guidelines – LAMAs and/or LABA + seasonal influenza vaccination + one-off pneumococcal vaccination – for disease maintenance and prevention of exacerbations.

– When a COPD patient has an exacerbation, the pharmacological therapy is somewhat consistent: antibiotics, corti-

In patients with FEV1/FVC <0.70:

GOLD 1:	**Mild**	**FEV1 ≥80% of predicted**
GOLD 2:	**Moderate**	**50% ≤ FEV1 <80% of predicted**
GOLD 3:	**Severe**	**30% ≤ FEV1 <50% of predicted**
GOLD 4:	**Very severe**	**FEV1 <30% of predicted**

TAB. 3

COPD
– Classification of airflow limitation severity.
– Specific spirometric cut-points can be used.

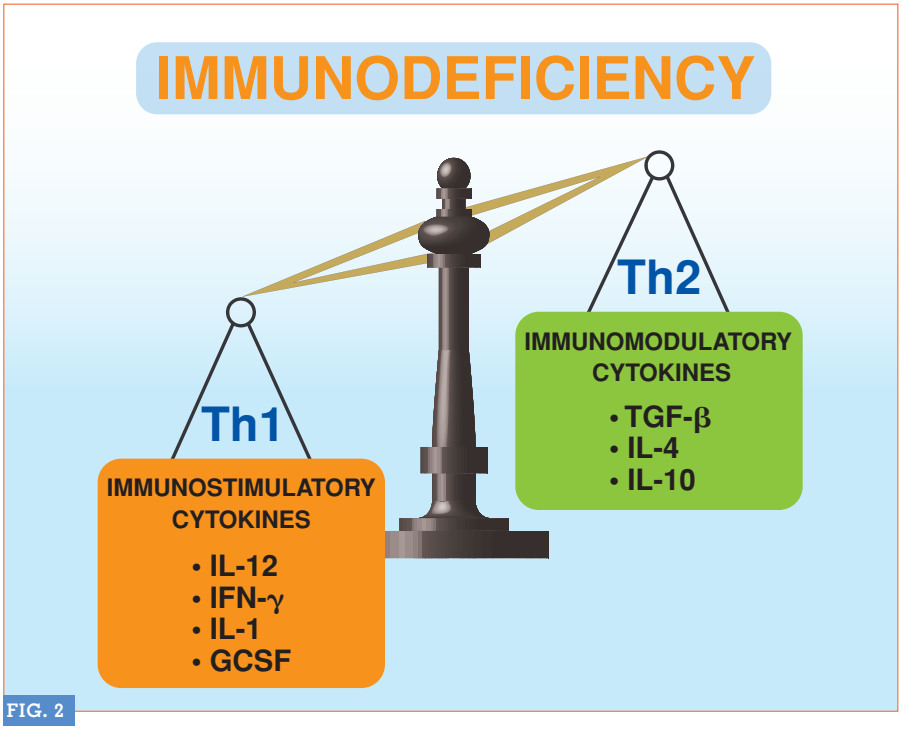


FIG. 2

sones by mouth and/or nebuliser + LAMAs and/or LABA, fluidifiers and expectorants, often combined with O_2 gas (especially when SAT values drop to between 82% and 90%).

– In this situation, the patient presents asthma-like symptoms, with dyspnoea and shortness of breath, as well as a persistent hacking cough, signs of bronchiolitis (involving the lesser airways) and bronchospasm of the same with severe airflow limitation.

This condition is extremely familiar to general practitioners **(GPs)**, who know that therapeutic intervention must be swift and aimed at evaluating whether the patient can be treated at home or whether hospitalisation is required, especially when patients present comorbidities that may complicate the clinical situation.

The more frequent the exacerbations, the more medicinal products (especially antibiotics and steroids) required and the more exposed the patient is to recurrences, due to the down-regulation of the Th1 side of the immune balance (FIG. 2) with inappropriate innate immune response induced by the pro-inflammatory cytokines TNF-α, IFN-γ and IL-1, which constitute this side of the balance.

It also goes without say that during the exacerbation phase, due precisely to the complexity and instability of the clinical setting, there is no place for either Bioregulatory Systems Medicine - **BrSM**, or for Physiological Regulating Medicine - **PRM**.

TAB. 4

Can **BrSM/PRM**
• prevent exacerbations?
• reduce use of medicinal products [antibiotics (resistance), cortisones]?
• help maintain prescriptive appropriateness in compliance with the national and regional budgets established for general medicine?

– I asked myself whether this might be useful in reducing the number of exacerbations; this would obviously have made it possible to use less antibiotics and cortisones, with a doubtless advantage for the patient, who would experience fewer side effects and less bacterial resistance, which is increasingly frequently reported due to excessive, and often inappropriate, use of these drugs. Furthermore, it would make it possible to ascertain whether using BrSM and PRM in this way might help GPs in the management of prescriptive appropriateness in order to meet national and regional targets *(spending review)* (TAB. 4).

MATERIALS AND METHODS

The study was conducted on a population of patients with COPD, some of whom with concomitant bronchiectasis (confirmed diagnosis in accordance with the GOLD guidelines).

– The study enrolled **12 patients** (6 M; 6 F, aged 54 - 99 years, mean age 75.5 years); 4 patients were GOLD stage 2 and 8 patients were GOLD stage 3; of whom 5 with concomitant bronchiectasis.
The patients were split into 2 groups (FIG. 3):

- **Group A**: **6 patients**, mean age 74.1 years, who received LAMAs and/or LABA + influenza vaccination + pneumococcal vaccination.
  2 GOLD stage 2 patients, **4** GOLD stage 3 patients; **2** patients with concomitant Bronchiectasis.
- **Group B**: **6 patients**, mean age 77.0 years, who received LAMAs and/or LABA + influenza vaccination + pneumococcal vaccination + **preventive overlapping therapy with BrSM** and **PRM**.
  2 GOLD stage 2 patients, 4 GOLD stage 3 patients; **3** patients with concomitant bronchiectasis.

The observation started in September 2015 (T0) and ended in March 2019 (T6). As indicators, the following were

taken into account: **1)** the demand for home/ambulatory visits; **2)** prescriptions for antibiotics and corticosteroids; **3)** treatment days.

The BrSM and PRM therapy prescribed to Group B (FIG. 4) consists in medicinal products for the treatment and prevention of colds:
Guna-Flu, 1 dose/week, taken in October, November, January, February, April, and May;
Citomix, 5 granules/day, taken from October to May;
Guna-Anti IL 1 and **Guna-IL 10**, 20 drops of each medicinal morning and evening from October to May; these medicinal products were prescribed with the aim of restoring the immune balance (stimulation of the Th2 side);
Echinacea compositum s, Ubichinon compositum, Coenzyme compositum®, 1 vial of each multicomponent-multitarget medicinal product by *mouth* via the sublingual route, on waking in the morning, once a week from October to May.

RESULTS

The following data were recorded regarding the **demand for home/outpatient clinic appointments** during the years of observation (FIG. 5):

Gruppo A (LAMAs and/or LABA):
▶ **80** outpatient/home appointments over 5 years
▶ average **16** appointments/year
▶ **2.66** appointments per patient/year.

Group B (LAMAs and/or LABA + BrSM and PRM medicinal products):
▶ **36** outpatient/home appointments over 5 years
▶ average **6** appointments/year
▶ **1** appointment/patient/year.

During appointments, patients were prescribed medicines, especially antibiotics and cortisones, in order to rapidly reduce the septic state-inflammatory agent causing the bronchiolitis and changes in airflow in the lesser airways responsible for the acute symptoms with considerable distress for the patient, dyspnoea, cough, and malaise.

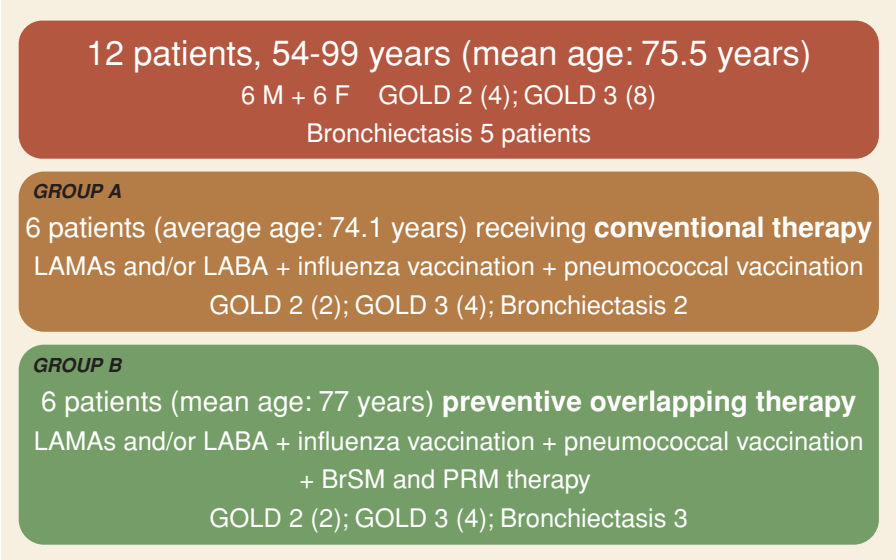


FIG. 3

• Data regarding the **prescription of antibiotics** (FIG. 6):

Group A (LAMAs and/or LABA):
▶ **71** packs prescribed over 5 years
▶ **308** days of therapy over 5 years
▶ **10.3** days of therapy/year/patient.

Group B (LAMAs and/or LABA + BrSM and PRM medicinal products):
▶ **17** packs prescribed over 5 years
▶ **90** days of therapy over 5 years
▶ **3.0** days of therapy/year/patient.

• Data regarding the **prescription of cortisones** (FIG. 7):

Group A (LAMAs and/or LABA):
▶ **35** packs prescribed over 5 years
▶ **200** days of therapy over 5 years
▶ **6.6** days of therapy/year/patient.

Group B (LAMAs and/or LABA + BrSM and PRM medicinal products):
▶ **7** packs prescribed over 5 years
▶ **45** days of therapy over 5 years
▶ **1.5** days of therapy/year/patient.

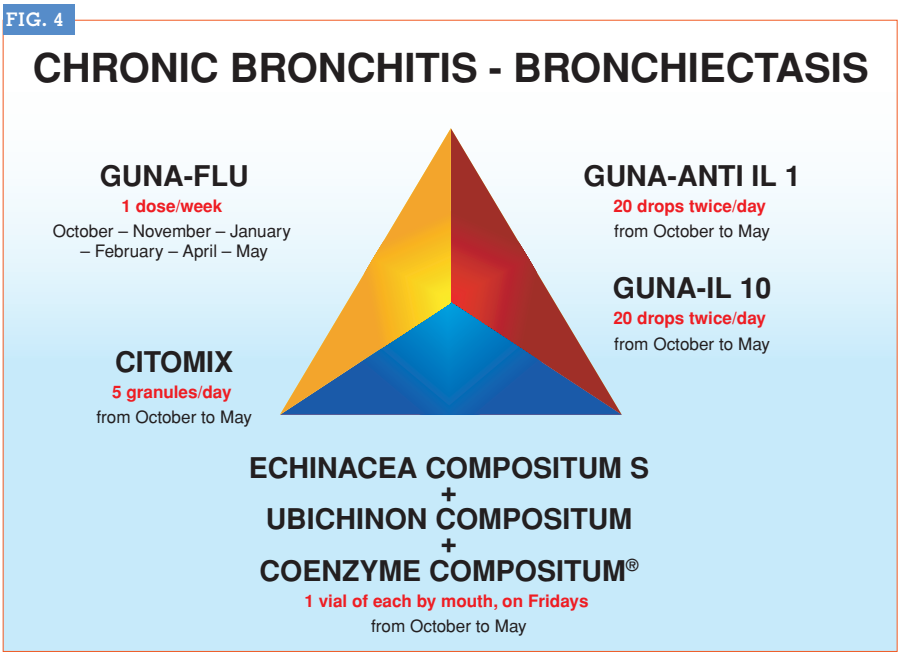


FIG. 4

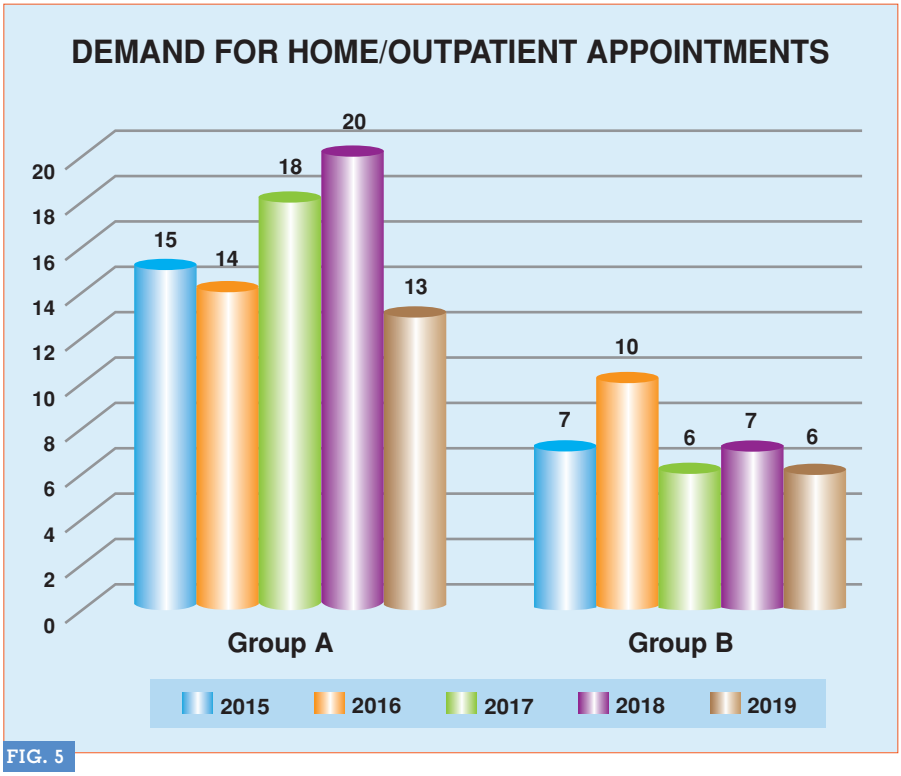


FIG. 5

The other indicators considered were **1)** prescriptive appropriateness **2)** compliance with national, regional and hospital pharmaceutical budgets, general practice governance targets, with which all general practitioners are familiar and for which they are monitored by the competent authorities.

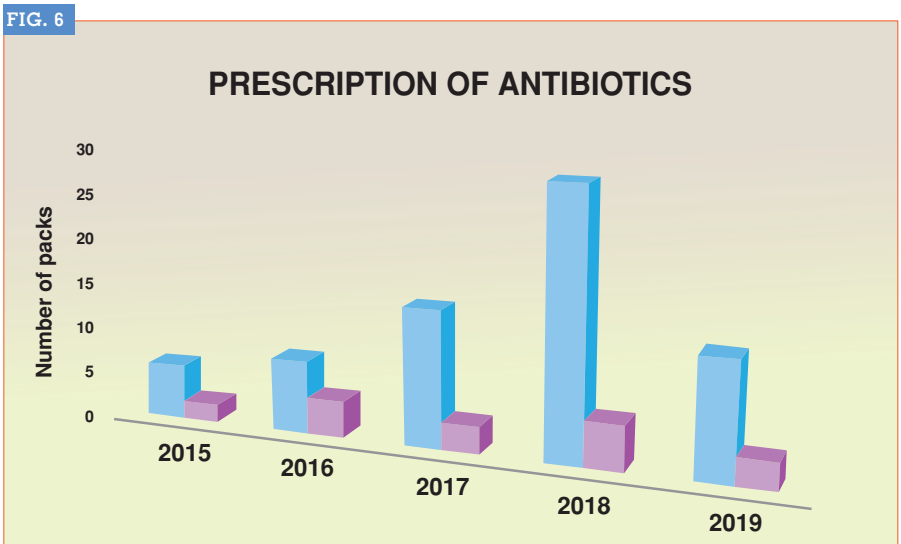
Keeping the healthcare budget under control means keeping the overall Regional budget under control, as **80%** of the entire Regional budget is allocated to healthcare (TAB. 5).

Incidentally, in the region of Umbria where I practice, pharmaceutical prescriptions can only be issued by general practitioners; specialists are merely able to suggest therapeutic indications, but they cannot personally prescribe them using regional or NHS prescriptions.

The *pro capite* pharmaceutical spending target set by Umbria Regional Authority for 2018 was EUR 180.00; the spending target established by Umbria 2 Local Health Authority for the same year was EUR 154.00.

The Umbria 2 Local Health Authority website indicates some of the classes of medicinal products prescribed; the "general antimicrobial agents", class consists primarily of "antibiotics"; personal prescriptions are considerably lower than the average for Umbria 2 LHA **(about 1/3 lower)**, most likely as a result of a different prescriptive behaviour influenced by personal training in BrSM and PRM.

FIG. 6



	2015	2016	2017	2018	2019
Group A	6	8	15	29	13
Group B	2	4	3	5	3

CONCLUSIONS

As mentioned previously, in the COPD exacerbation phase, as in the acute phase of other degenerative diseases, there is no place for BrSM and PRM; however, this does not preclude their use in the **prevention** of the **exacerbations** of these conditions.

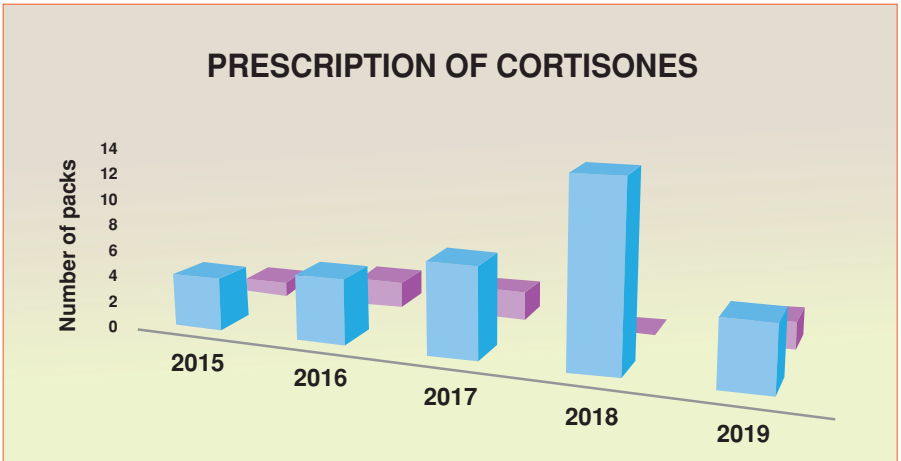
Multicomponent-multitarget and PRM medicines make it possible to act on homeostatic regulation systems by restoring the immune balance and actually reducing inflammation, with a positive effect on the number of COPD exacerbations.

– By doing so, it is possible to limit the medicinal products required during the acute phase of the disease:
less antibiotics and less cortisones, with fewer side effects and a reduced risk of antibiotic-resistance.

It goes without say that this does not mean not using antibiotics when they are necessary, rather avoiding an excessive and often inappropriate use of these medicinal products.

Using fewer medicinal products (antibiotics/cortisones) also means making the patient prone to fewer recurrences, as these medicinal products can contribute to reducing the innate immune response mediated by TNF-α, INF-γ and IL-1, which constitute the Th1 side of the balance, that in these situations can cause cytokine down-regulation.

– GPs who use BrSM and PRM in their clinical practice obtain better results in terms of patients' quality of life (for the reasons outlined above) and are facilitated in complying with the parameters of prescriptive appropriateness established for the national and regional spending budgets.



	2015	2016	2017	2018	2019
Group A	4	5	7	14	5
Group B	1	2	2	0	2

FIG. 7

TAB. 5

RESULTS

- Prescriptive appropriateness and compliance with national, regional and LHA pharmaceutical spending budgets are expenditure governance objectives: regional and national law.
- (< EUR 180.00 pro capite region of Umbria; < EUR 154.00 pro capite Umbria 2 LHA - 2018).
- 80% of the regional budget is dedicated to spending on healthcare.
- In the region of Umbria, pharmaceutical prescriptions can only be issued by GPs; specialists can merely suggest therapeutic indications, but cannot personally prescribe them using regional or NHS prescriptions.

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Fig. 1
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author

Dr. Alberto Trippetti
– Specialist in Endocrinology
– MMG USL Spoleto (PG), Umbria2
Spoleto (PG), Italy