

Long summaries / Riassunti estesi

“COPD a social disease: inappropriateness and pharmaco-economics.  
The role of the specialist: present and future”

Venice, Italy, April 21-22, 2010

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**Conference: "COPD a social disease:  
inappropriateness and pharmaco-economics.  
The role of the specialist: present and future",  
Venice, April 21-22, 2010: long summaries**  
Conferenza: "BPCO una malattia sociale:  
inappropriatezze ed aspetti farmacoeconomici.  
Il ruolo dello specialista: presente e futuro",  
Venezia, aprile 21-22, 2010: riassunti estesi

Edited by Claudio F. Donner

## Rationale and structure of the conference

### Razionale e struttura della Conferenza

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Chronic respiratory diseases (CRDs), with particular regard to COPD, constitute an epidemic in the full sense of the term, though they still go underdiagnosed and undertreated. COPD is one of the major health problems worldwide, negatively affecting patients and their families, the employment sector, the institutional network and, hence, society as a whole. Its epidemiological, clinical, social and socio-economic impact is on the rise and there are no signs of any change to this trend.

The Global Alliance against chronic Respiratory Diseases (GARD) of the World Health Organisation (WHO) - of which AIMAR has been a partner since

2005 [1] - was launched in 2006 as “a voluntary alliance of national and international organizations, institutions and agencies committed to the vision of a *“world where all people can breathe freely”* [2,3]. The goal of GARD is to improve global lung health by promoting a comprehensive approach to fight CRDs within the framework of the WHO strategic measures [4].

GARD has formulated the following working recommendations:

- to develop national programs of prevention and control of CRDs, with the double aim of defining the most pertinent strategies and healthcare

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actions and raising political and social awareness about this public health priority. The first step to attain this goal are health education campaigns and data collection on: the frequency of these diseases, their impact, and the relative risk factors;

- to provide training and continuing education on prevention and treatment of CRDs, disseminating the existing guidelines;
- to facilitate access to essential treatments and favour adherence to long term treatment, including drug treatment and pulmonary rehabilitation, particularly amongst disadvantaged sectors of the population.

Besides GARD recommendations to create synergies on prevention and control between CRDs and other chronic diseases, the final outcome should be country-specific initiatives tailored to local needs. Therefore, after the first phase, from 2006 to 2008, devoted to building a global network, consolidating objectives and creating tools and resources, the second phase (started in 2008 and due to end in 2015) has as its aim to launch GARD national organizations in each country [5].

Pre-requisites for developing a GARD national body are as follows:

1. a prior analysis of the situation of surveillance, prevention and control of chronic respiratory diseases in that country;
2. invitation to the Ministry of Health to participate in the development of the GARD national body;
3. a similar invitation to the WHO Regional Office and WHO country representative.

In Italy, all three pre-requisites were fulfilled in June 2009 when GARD-Italy was launched in Rome, during a meeting addressed by the Minister of Health, Ferruccio Fazio [6] in which a Document of Strategy [7] was signed by all the major medical and patients' societies and associations attending the meeting. AIMAR signed this document and viewed it as the first endpoint of numerous initiatives carried out by AIMAR to implement GARD in Italy (seminars, learning courses, conferences, documents, recommendations, all aimed at emphasising the importance of respiratory diseases and disseminating the existing guidelines for their management). Among the actions which a GARD national body is urged by WHO-GARD to carry out, one is to recommend affordable and effective strategies for the management of CRDs based on the latest evidence [8]. Another is to provide training and continuing education on the prevention and treatment of CRDs, disseminating the existing guidelines, while emphasizing the sustainability of all the recommended actions.

In face of the need to reconcile the limited available

economic resources with the increasing demand for well-being, the health services of industrialized countries are at present devoting much attention to the costs generated by healthcare in their own territories. CRDs, in particular, concern a large number of subjects and generate important health and social costs. The global impact of these diseases, in particular COPD, has been the subject of an increasing number of pharmaco-economic studies published in the literature in recent years. Although these studies had different experimental designs, they all confirm the growing impact of COPD in all countries, both from the perspective of the patient and patient's family, and that of society as a whole. The findings that emerge reveal that the attitude towards COPD management is still largely inadequate. This Top Seminar, starting from the above scenario, focuses on the role that the pulmonary specialist can play in detecting inappropriateness in the clinical course of COPD and in providing the basis for a correct assessment of pharmaco-economic issues. Given the increasing social impact of COPD, the meeting fits in perfectly with the goals and recommendations of GARD.

**"COPD a social disease: inappropriateness and pharmaco-economics. The role of the specialist: present and future"** has been organized by AIMAR under the umbrella of the 'Year of the Lung 2010' promoted worldwide by the Forum of International Respiratory Societies and within Europe by the European Respiratory Society. AIMAR has designed this new Top Seminar as a moment for all the stakeholders (Ministry of Health, health district managers, patient organizations and specialists in respiratory medicine) to come together and reflect on the pharmaco-economic issues related to the clinical course of COPD.

The Seminar will be divided into four sessions:

1. From scientific to social and institutional recognition: comparing different experiences.
2. Pharmaco-economics.
3. Inappropriateness at different steps of management.
4. A new decade of COPD.

In each session, leading international scholars of COPD will discuss with the other stakeholders not only the scientific issues, but also the impact - present and future - of COPD from the point of view of the patient, their family and society as a whole. The Seminar will produce a series of documents (e.g. a short report to be published in *Respiratory Medicine*, and full proceedings in *Multidisciplinary Respiratory Medicine*, AIMAR's official journal) which will be useful for GARD-I to plan and implement actions so as to make Italy a country "where all people can breathe freely".

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## Future of NHS in the welfare state

### Il futuro del Servizio Sanitario Nazionale nel "welfare state"

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The National Health Service (NHS) has up till now guaranteed health care to all citizens along with a constant rise both of the average life expectancy and of individual wellbeing. In a certain sense, however, the NHS is today a victim of its own self: in the last fifty years – following progress in medicine and in the organization of the social state – Italy (as other developed countries) has seen a radical change in what constitute the prevalent diseases and main causes of death, and this change has thrown the NHS into crisis. The chronic invalidating diseases that dominate the scene today cannot be managed with the old hospital-centered model that was based on the need to respond to acute situations: the system has to be readapted to the actual epidemiological situation today.

The health care provided for chronic bronchopulmonary diseases, lung cancer and cancer in general, for diabetes and heart diseases (to mention just a few of the most frequent and important diseases) is becoming increasingly costly (as new pharmacological and rehabilitative therapies are introduced and patients survive longer) and the number of people affected by these diseases is destined to rise substantially as the average age of the population rises. These tendencies could in the medium term render the cost of health unsustainable and, in the absence of corrective re-equilibrating measures, health costs might more than double by 2050. For this reason a radical change in the organization of the NHS is necessary, in harmony with a change in the role played by the state.

In the 19<sup>th</sup> and first part of the 20<sup>th</sup> century, the prevalent diseases were infective diseases of an epidemic nature (such as cholera, tuberculosis, poliomyelitis) and the role of the state was in the first place to guarantee drinkable water, sewage disposal and improved living conditions, and successively to help defend the population through programs of mass vaccination against diseases not eliminated by the improved public hygiene. Today the diseases are linked to life styles chosen on an indi-

vidual basis, not to collective living conditions, and hence the role of the state is no longer to choose and implement the best health options *on behalf of* citizens but rather to help citizens themselves choose the best options, through education, health information and the provision of integrated services of primary, secondary and tertiary prevention.

The future of the NHS will thus be focused on **primary prevention** (helping citizens to prevent the onset of diseases) and **early diagnosis and rehabilitation** (helping citizens to reduce the invalidating consequences of already existing diseases with the least possible impact on the community). It goes without saying that the need for a radical change in health care for reasons of sustainability, already announced in previous years, has now become absolutely urgent with the heavy crisis that has recently hit the world economy.

These changes in the NHS will take place within the context of an overall change in the whole welfare system, centered on the idea that people first try to develop their own resources to respond to their needs, that people live in a free and responsible manner and respond to their own uncertainties. In other terms, in the new welfare, the concession of protection and subsidies will be subject, where possible, to the citizen's active participation in society through a path that ensures opportunities while stimulating the individual's own responsibility.

The link between health and social wellbeing is indissoluble: just as health promotion reduces poverty, emargination and social distress and increases work productivity, employment rates and overall economic growth, so too does an increase in the quality of work and work opportunities over a longer life span, and a context that favours employability and social mobility - whatever the individual's starting point - translate into greater health and psycho-physical wellbeing. The new welfare must orient people towards active behaviours and responsible lifestyles, preventing situations of need due to physiological (infancy, materni-

ty, old age) or pathological (disease, accident, disability) events or to particular economic situations (business or employment crises, unemployment, termination of work). In this context, *health* does not mean simply treating the disease but rather *a priori* promoting wellbeing and developing personal capacities, taking into account the different conditions of each individual.

The citizen's active participation, a correct information and health culture, essential in an era of great changes, a renewed relationship of trust between family doctor and patient, are the premises for promoting **healthy life in the active society** (which also is – not by chance – the title of the white book on the future of the social model recently produced by the Ministry. The physical setting in which the changes described above will take place is the **local community**, i.e. the place where the integrated, preventive responses to people's real and potential needs are put into effect, where the policies designed to guarantee the continual employability of people are implemented, so preventing their exclusion from the employment market; and, finally, where the social-health services aimed at prevention, early diagnosis, primary care, and home care are developed.

What will have to be achieved as rapidly as possible is a unified management of the homogeneous socio-health-welfare services at local level, able to create a *continuum* between systems for health care and those for social protection; a unified management that sees the socio-health districts as the citizens' center of reference and the place where this integration occurs in effect.

In the NHS, one will have to go beyond the concept of "integration" between hospital and local community in favour of a new interdisciplinary and interprofessional approach with the person at the center of the treatment process (which must flow without interruptions), utilizing a personal electronic dossier that contains all relevant information about the person. In this vision, the hospital will return to its "historical" role as a provider of emergency and acute care while the general practitioner (GP), operating no longer as a "soloist" but in association with other professionals in a collaborative network, will be the stable point of reference for the patient throughout the course of the day and week. Addressing an international audience of respiratory specialists, I cannot but conclude with some remarks of particular reference to specialists, focused on the application of the new model of welfare to respiratory medicine. I greatly appreciate the fact that the title of your Seminar is related to the "social" aspects of the most important chronic respiratory disease and that you particularly wish to examine the specialist's role in the appropriateness of interventions and in the "pharmaco-economics" of management.

Respiratory diseases constitute an emergency. In Italy, all together (including also lung cancer) they represent the second most important cause of death and their frequency and diffusion is probably far

greater than we actually realize, given that they are widely under-diagnosed. Underdiagnosis has not only epidemiological but also clinical consequences: as little attention is paid to respiratory diseases by the individual and by the community, those affected receive late and non optimal treatment. A further consequence of the poor visibility that up to now has characterized respiratory diseases is that insufficient consideration is given to the specialist hospital structures dedicated to them. However, signs of the new importance now being attributed to respiratory diseases are the fact that the Italian National Health Plan 2006-2008 placed chronic respiratory diseases among its four top health priorities and that the Ministry of Health launched in 2009 - when I myself was Minister of Health - GARD-Italy, the Italian part of the Global Alliance against Chronic Respiratory Diseases (GARD) of the World Health Organization (WHO), a voluntary alliance of national and international organizations, institutional bodies and agencies that has as its goal to reduce the global burden of chronic respiratory diseases.

It is precisely this recognized importance that prompts us to denounce the critical situation that exists at present. Patients suffering from chronic pulmonary diseases are treated in a discontinuous and non integrated mode: this leads to inappropriateness of the caring procedures. This inappropriateness represents a cost that is not negligible. The Institute for the Innovation and Improvement of the NHS in Britain evidenced, for example, that GBP £1.3 billion are spent each year in visits to Emergency Care for patients with 18 diseases ([www.healthcarecommission.gov.uk](http://www.healthcarecommission.gov.uk)).

These include up to three or four visits per year by the same patient. Not by chance, occupying first place in the list of diseases is chronic obstructive pulmonary disease (COPD), with more than 106,000 admissions and an annual cost of £253 million, while in third place, after angina pectoris, comes asthma with more than 61,000 admissions and a cost of £64 million. Varying percentages of these admissions resulted inappropriate at a retrospective analysis. An optimal management of the above diseases would not only reduce the crowding of Emergency Care facilities and lower the global health costs, but it would improve also the conditions of life of those affected.

At the organizational level, the health care for chronic respiratory diseases will be similar to that for diabetics. One must achieve a greater possibility of self management for the patient, give more responsibility to the GP, with an opportune use of telemedicine and home care built into the plan.

In the field of pulmonology, the NHS must undertake in each ULSS to:

1. prevent respiratory disease developing through a consistent reduction of the number of smokers in the community;
2. improve COPD diagnosis, in particular through a more widespread use of spirometric tests;
3. help patients to self manage their own disease,

through pulmonary rehabilitation;

4. integrate the care of patients affected by COPD, i.e. link specialist care to primary care, and extend end of life treatment from the oncological to the respiratory sphere.

Within the strictly hospital setting, the role of Pneumology will be similar to that of modern cardiology: intensive management of acute respiratory problems and consultancy and specialist guidance provided within the local community. In terms of this project each Operational Unit will have to organize itself.

On this subject, I would like to cite an experiment that is underway in the area I come from. It is an initiative in pulmonary rehabilitation on patients affected by COPD, which involves, besides respira-

tory specialists and GPs, also sports physicians and graduates in motor science. This initiative is being carried out completely in the local community and has so far enrolled 50 patients, who have been offered the possibility of strength re-education. What is news for you who are specialists in the field is not so much the fact that all the participants have increased their performance and improved their quality of life, but that this has all occurred through a multidisciplinary effort and completely *outside* of the hospital setting.

I hope that this Seminar will bring other significant gains to help individual specialists better understand the existing problems and better define their own role.

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## The growing role of rehabilitation and chronic care Il ruolo crescente della riabilitazione e del trattamento cronico

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### Definition and background

Pulmonary rehabilitation is an evidence-based, multidisciplinary and comprehensive intervention for patients with chronic respiratory diseases who are symptomatic and often have decreased daily life activities. Integrated into the individualized treatment of the patient, pulmonary rehabilitation is designed to reduce symptoms, optimize functional status, increase participation, and reduce health care costs through stabilizing or reversing systemic manifestations of the disease [1].

*Extensive rehabilitation:* "Complex welfare activity for patients who have superceded the acute and immediate post-acute phase and require interventions to ensure further functional recovery in a defined time" (DRG 398/2000).

*Rehabilitative maintenance activities:* "Assistance activities aimed at patients with stabilized outcome from psycho-physical disease requiring interventions to keep any residual capacity functional or to contain the damage" (DRG 398/2000).

### Aim

Specific aims of pulmonary rehabilitation are to reduce symptoms, teaching patients to deal successfully with their disease, to maintain an active and independent lifestyle, to maximize functional abilities, to reduce the consumption of healthcare resources and, where possible, to improve survival [2-4].

### Materials and methods

Pulmonary rehabilitation programs involve patient assessment, exercise training, education, nutritional

intervention and psychosocial support. Pulmonary rehabilitation includes a spectrum of interventional strategies integrated into the lifelong management of patients with chronic respiratory disease and involves a dynamic, active collaboration among the patient, family and health care providers. These strategies address both the primary and the secondary impairments associated with the respiratory disease [1].

The rehabilitation program includes optimizing the drug therapy, education, chest physiotherapy, exercise training, respiratory muscle training, selective muscle group training, occupational therapy, reducing workload of the respiratory muscles, long-term oxygen therapy, psychosocial and nutritional programs [5,6].

These programs are aimed at patients with the following diseases: COPD, asthma, cystic fibrosis, bronchiectasis, chronic respiratory failure (CRF) from any cause, severe acute respiratory patients with CRF, restrictive syndromes from neuromuscular and chest wall diseases, pulmonary fibrosis and other interstitial disease, pre- and post-surgery, outcomes of chest injury, respiratory sleep disorders, outcomes of pulmonary embolism, chronic pulmonary heart disease, preparation and management of lung transplantation [7-9].

Pulmonary rehabilitation programs can be performed:

- at *home*: usually they follow the inpatient and outpatient programs; interventions are designed to keep the patient at the highest level of sufficiency;
- in *day hospital* and/or the *outpatient setting*: activities that tend to reduce impairments report-

- ed by the subject consequent to an acute event;
- in *hospital*: patients with no or limited mobility who need continuous monitoring and invasive maneuvers, or with transport difficulties.

An example: COPD (Figure 1).

Patients with COPD are a group of high consumers of healthcare resources in terms of drugs, hospital admissions and days spent in hospital: in a study conducted in Italy on moderate to severe COPD patients hospitalized due to exacerbation, health care rehabilitative treatment was only €42 per patient/year, i.e. 0.9% of all direct costs. Despite this, one of the potential benefits of rehabilitation would be to reduce episodes of exacerbations and, as a result, health spending [9-10].

Rehabilitation programs have been shown to reduce hospitalizations and home visits and the number of exacerbations [11]. Clini has demonstrated that a cycle of rehabilitation included in a shorter hospitalization stay resulted in the same physiological effects as a longer cycle in day-hospital, but had lower costs [12].

### Organization, setting

While many protocols have been evaluated to render respiratory rehabilitation more efficient in various lung diseases, few studies have focused on the optimal composition of the staff, organization of the place of care and equipment [13]. Respiratory rehabilitation is a multidisciplinary intervention, in which the following health professionals collaborate:

- pulmonologist, who should have the role of pro-

- gram director
- nursing staff
- rehabilitation therapists (nine different types recommended).

### Areas of rehabilitation treatment and types of patients:

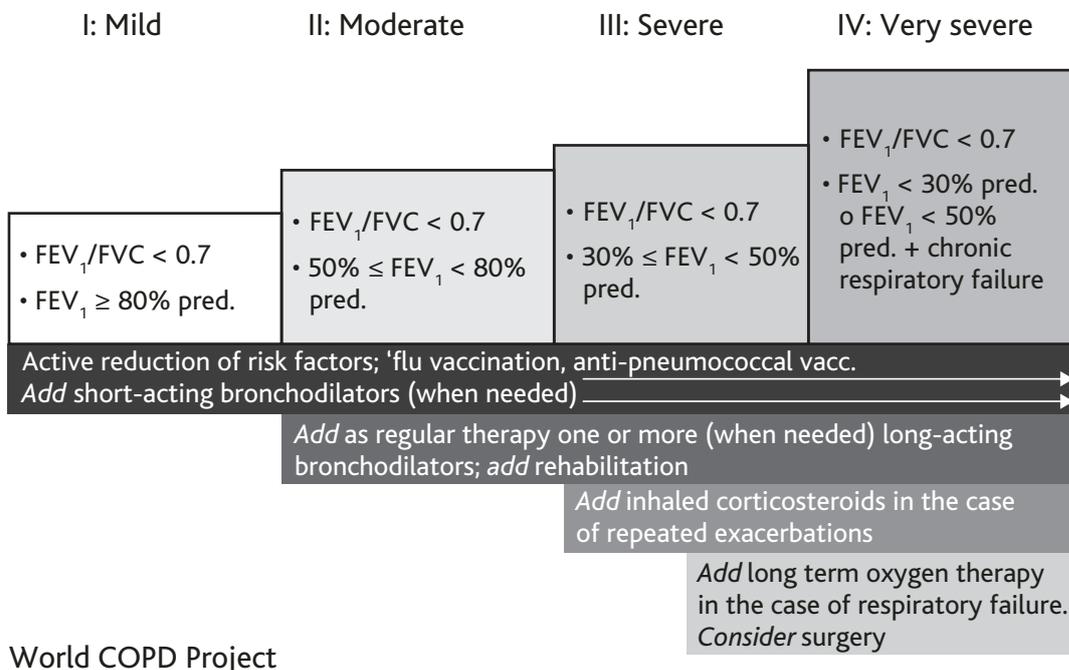
1. Respiratory Intensive Care Unit and general ICU
2. Pulmonary diseases department
3. Pulmonary rehabilitation in pre- and post-thoracic and abdominal surgery
4. Pulmonary rehabilitation in pre- and post-transplant of thoracic and abdominal organs (lung, heart, liver, etc.)
5. Respiratory rehabilitation in diseases characterized by muscle weakness (neuromuscular disorders)
6. Respiratory disease in children [14].

### Existing models

At present the organizational models and the rehabilitation programs are not very uniform.

1. The model used in some foreign countries (USA, Canada, Brazil) and in some Italian hospitals is that physiotherapists form a functional team with the other professionals; they are always present, in ICU and in the Emergency Room, covering the entire day, every day of the week and (only abroad) with shifts even at night.
2. Another organizational model, often found in Italy, provides for the presence of physiotherapists within a single department, or throughout the

FIGURE 1: COPD TREATMENT BASED ON DISEASE STAGE



Tratto da [15] mod.

entire hospital, especially if this is dedicated to specific diseases. Here the physiotherapist carries out his/her duties, often working alongside other professionals with activities during the day for 5 days/week. These structures also provide outpatient treatment for external or discharged patients (e.g. regional centers for cystic fibrosis and other centers dedicated to pediatric, orthopedic, neuromuscular disease, and many rehabilitation centers in agreement with the National Health System).

3. A third model envisages a pyramid structure, in which physical therapists address all needs; it provides all the benefits of rehabilitation "on demand" as requested by the other operating units. Rehabilitation treatment is interrupted when the patient is discharged, and the physiotherapist moves on to deal with a new case that is assigned [14].

### Results and conclusions

Pulmonary rehabilitation is undergoing great development. Since the publication of previous recommendations there has been significant progress in both techniques and outcome assessment [13]. The new data give further support for:

- the benefits of training in improving lower limb dyspnea and quality of life. There are no definitive studies on the effect on survival, costs and utilization of resources;
- other studies have evaluated upper limb training as a means to obtain benefits in daily living activities, but the results do not offer sufficient evidence for its introduction as a routine practice;

Data are also emerging on the effects of rehabilitation on respiratory diseases other than COPD.

Important areas for future research concern [13]:

- the length of the programs and strategies to maintain the benefits obtained;
- more efficient use of scarce resources;
- individualization of the program to different phenotypes of clinical COPD;
- better definition of optimal training schemes;
- the supplementation of oxygen in various situations of hypoxemia (resting, stress, night);
- the use of non-invasive ventilation;
- nutritional supplementation;
- electrical stimulation of muscles and peripheral respiratory muscles;
- the role of exacerbation to influence results of rehabilitation and viceversa.

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## Session I: From scientific to social and institutional recognition: comparing different experiences

Sessione I: Dal riconoscimento scientifico a quello sociale ed istituzionale: comparazione di diverse esperienze

### The institutions Le Istituzioni

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The incidence of chronic respiratory disease has increased steadily over the past several years and currently constitutes a serious public health problem. Chronic respiratory diseases are often underdiagnosed. Many patients are not diagnosed until the chronic respiratory disease is so severe as to prevent normal daily activities, including attendance at school or work.

The prevention of chronic disease, particularly of chronic respiratory diseases, and the reduction of their social and individual impacts is based on the modification of environmental and social factors, and the improvement of diagnosis and treatment. Today, many risk factors have been identified: tobacco smoke, allergens, occupational agents, indoor air pollution and outdoor pollution. Prevention of these risk factors will have a significant impact on morbidity and mortality.

In a country such as Italy, where life expectancy is continuously rising, it is important to set up respiratory disease preventive measures, in order to achieve better health conditions and preserve the population's quality of life.

The Italian Ministry of Health has made respiratory disease prevention a top priority and has been gradually putting in place a comprehensive strategy. It has a role in the implementation of policies against tobacco smoking, indoor and outdoor pollution, obesity, and communicable diseases. Presently, these actions are not well integrated, and this poor coordination is an important limitation for the Ministry of Health. Therefore, the GARD initiative is

a great opportunity for the Ministry of Health which may play a role in coordinating GARD in Italy. Following the WHO-GARD guidelines, we have collaborated in the creation of the Italian GARD.

**The main objective** is to discuss the development of a global chronic respiratory disease program in Italy. Effective prevention implies setting up a health policy with the support of health care professionals and citizen associations at the national, regional, and district levels. What is required is a true inter-institutional synergy: prevention of respiratory diseases cannot and should not be the responsibility of doctors alone, but should involve politicians/policy makers, as well as the media, local institutions, school, and food producers.

GARD could be a significant experience and a great opportunity for Italy, and a means to implement the GARD vision of a "world where all people can breathe freely".

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## Role of patients' associations

### Il ruolo delle Associazioni di pazienti

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The right to health, as defined in the Italian Republic Constitution, is one of the fundamental rights of an individual.

The search for different, new equilibria in which it is the individual, and not the disease, at the centre of the system, requires a greater responsibility on the part of all the players involved, including the patients, to achieve the goal of preventing or delaying the development of complications.

Therefore, interventions must be coordinated among scientific societies, professional associations, volunteer organisations, and public and private institutions. It is thus necessary to develop assistential profiles based on a multidisciplinary approach and ensure continuity among actions of prevention, treatment and rehabilitation, with intersectorial interventions, both medical and social, able to involve also

the family and volunteer organisations.

In the approach to chronic diseases in general, and to COPD in particular, we must work to empower the people, i.e. make them able to participate actively in the therapeutic choices that concern them and in the decisional processes aimed at improving their quality of life and reducing complications. Patients must be helped to obtain "ability" through acquiring knowledge about the disease and treatments available. Indeed, knowledge is essential to obtain a good level of healthcare that places the patient at its centre. On the other hand, it is also necessary that the health care system and social services are aware of people's needs, and are able to work together to trigger a process of improvement, that respects the rights and freedom of the individual.

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## Primary care

### Medicina di base

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Due to its increasing prevalence, COPD is considered a social disease which warrants special attention at primary care level. General practitioners (GPs) have a central role in disease prevention, detection, treatment, and management. This applies also to COPD. Smoking cessation intervention is the cornerstone for preventing COPD: GPs' attitude towards offering brief advice to every smoker in the office is becoming a rule, as well as their awareness to belong to the wider network of anti-smoking services. The manifold contacts on a yearly basis with their patients who smoke allow GPs to carry out early detection by means of spirometry, and to collaborate with pneumologists if needed. COPD treatment should be based on regular therapy with inhaled drugs (long-acting bronchodilators and steroids) to ensure a good quality of life. Prevention

and treatment of exacerbations is of the utmost importance: avoiding airborne pollutants (environmental tobacco smoke and urban pollution) is mandatory, while early recognition of an exacerbation, and starting oral steroids and antibiotics courses, are the cornerstone of good practice by GPs. Finally, COPD management is based on planning regular clinical and functional follow up.

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# Role of the respiratory specialist

## Il ruolo dello specialista di ambito respiratorio

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Respiratory diseases constitute an emergency. Altogether (including lung cancer) they represent the 2<sup>nd</sup> major cause of mortality and are likely even more frequent than we know given the under-diagnosis that today exists [1-2]. The future trend is for a still further increase, although differentiated for the different diseases [3]. As for other chronic diseases, we need to re-think the organization of health care provided for respiratory diseases. Specialists need ongoing training not only on the "technical" front but also on health care planning, and must be informed about management and systemic issues based on solid epidemiological data or estimates.

### Background: respiratory diseases

*Cancerous diseases.* Lung cancer is everywhere one of the primary causes of cancer mortality [4]. Life expectancy at the time of diagnosis is low and has not substantially modified in the last decades due in part to the lack of procedures for early diagnosis [5].

*Chronic obstructive diseases.* These diseases (in particular, COPD and asthma) rank amongst the foremost causes of death and invalidity. COPD is very widespread, affecting at least 10-15% of the adult population [6]. It is estimated that COPD will rank 3<sup>rd</sup> as a cause of morbidity and 6<sup>th</sup> as a cause of mortality in 2020 [7]. The prevalence of asthma shows a wide variation among the different countries, ranging from 2-4% in the large Asian countries to 15%-20% in England, Canada, Australia and New Zealand [8]. In Italy, its prevalence is about 7% in children [9]. Asthma is moreover the most frequent occupational disease.

*Infective respiratory diseases.* In contrast to other specialist disciplines like gastroenterology, last century did not see a reduction in the morbidity due to infective respiratory diseases (pneumonia and tuberculosis being the most important). Today, the incidence of pneumonia ranges from 4.7 per 1000 inhabitants/year in the U.K. general population to 14 cases in the more elderly populations in Spain [10-11]; some countries have recently witnessed a rise in hospitalizations [12]. Tuberculosis is, after HIV infection, the 2<sup>nd</sup> most frequent cause of death from infective disease in the world [13].

*Obstructive apneas.* Obstructive sleep apnea syndrome (OSAS) is very widespread. The estimated prevalence in Italy is 2.7% of the adult population, though among males aged > 40 years it is 12% and for professional drivers it is 17% [14]. One of its

consequences is daytime sleepiness that can cause accidents, in particular driving accidents (22% of which are due to excessive sleepiness).

*Cigarette smoking.* The two most important respiratory diseases (lung cancer and COPD) are in the overwhelming majority of cases caused by cigarette smoking, which also worsens the disease course. Smoking is both a risk factor and a disease in itself. With variations between the different countries, smoking affects on average 1/4 to 1/5 of the population [15]. The specialist is involved in both its prevention and treatment.

### Economic and social costs of respiratory diseases

The total cost of respiratory diseases in Europe is more than €100 billion per year. COPD contributes to at least half of this figure, followed by asthma, pneumonia, lung cancer and tuberculosis. In general, inpatient hospital services represent 17.5% of the total cost, outpatient care 8.9%, pharmaceutical drugs 6.6%, mortality and rehabilitation 19.6%, and lost work days 47.4% [16].

The annual cost for medical treatment alone (direct healthcare costs) for a patient affected by COPD has been calculated in France to exceed €4,300, almost half of which is related to hospital admissions and one third to pharmaceutical drugs. The overall cost of COPD for France (based on a prevalence of 1.3%, and hence only very approximate, see below) has been estimated at €3.5 billion, i.e. 3.5% of the total medical expenditure [17]. Also the cost for the employer is elevated [17-19]. The social impact of COPD is very high, particularly in the phase of respiratory failure when the social life of the patient, now invalid, is reduced to zero.

The direct costs of asthma constitute 1-2% of overall healthcare costs in Italy. Indirect costs (concerning work and family) represent 60% of the overall costs. The cost/year of an adult asthmatic (aged 20-45 years) is estimated at €800 (with an incidence on family income between 2 and 8%). 11% of adult asthmatics and 19% of child asthmatics will be hospitalized at least once for asthma, and 19% and 31%, respectively, will require an emergency visit. Asthma in children is responsible for absence from school (31% of total school absences are related to asthma) and absence from work for the family.

### Trends in respiratory disease

Besides active smoking as the cause of the principal respiratory diseases, these latter are also linked to indoor and outdoor pollution (in the home, public places and workplace). Estimated trends over the

next few years are for:

- a rise in COPD (due to the increase of the average age and a decline in underdiagnosis), asthma (due to reasons not yet fully clear), and OSAS (due to an increase in the average body weight and a decline in underdiagnosis).
- stable trend for smoking (with country to country variations), lung cancer (in decline amongst males but on the rise amongst females), tuberculosis (dependent on the migratory flows), and pneumonia.

#### Role of the specialist in healthcare planning

To deal with chronic respiratory diseases and optimize their management, there is need for a global approach that can define, on the basis of solid epidemiological data, the best care for the patient throughout the course of the disease, in a way that is sustainable for the community.

Numerous initiatives and studies are under way everywhere. One of these, which for reasons of space we will focus on here, is the Global Alliance against chronic Respiratory Diseases (GARD), an ensemble of national and international organizations guided and coordinated by the World Health Organization (WHO): GARD's strategies and corresponding actions [20] delineate the role of the specialist at global and national level. For example, in Italy, the Ministry of Health – which defined chronic respiratory diseases as a priority of the national Health Program 2006-2008 and hence finalized, with the National Agency for Regional Healthcare Services (AGE.NA.S) the national guidelines for COPD – launched in 2009 GARD-Italy. [21]. Respiratory specialists participate in the “central” planning phase of all these initiatives, while other specialists participate in the “peripheral” phase of implementation. Successively, these same specialists verify the applicability in the real world and the final efficacy of what has been planned and implemented. Following we will see how.

#### Role of the specialist in implementing healthcare strategies

Today patients affected by chronic pulmonary diseases are managed in a discontinuous and non integrated mode with inappropriate care procedures as a consequence. In turn, the prevention of these diseases is neither systematized nor integrated.

Inappropriateness costs both the individual and the community. It has been calculated that GBP £1.3 billion are spent each year in the U.K. for Emergency Care visits for patients with 18 diseases (and 3-4 visits per individual patient). Occupying first place in the list of diseases is COPD and in third place is asthma. Varying percentages of these visits resulted inappropriate at a retrospective analysis [22]. An optimal management of the above diseases would not only reduce the crowding of Emergency Care facilities and the global healthcare costs, but would also improve the conditions of life of those affected.

The long term goal must be to reduce the incidence

of respiratory diseases while the short- and medium-term goal is to reduce - in an economically sustainable way – the social and economic consequences of the diseases already present, through a greater appropriateness.

The specialist thus has a role to play in primary prevention, early diagnosis and rehabilitation, as guide or coordinator or consultant depending on the type of intervention. The interventions to promote are [23]:

1. to prevent respiratory disease developing through a consistent reduction of the number of smokers in the community and total control of risk factors;
2. to improve and anticipate diagnosis, in particular of COPD and asthma, through a more widespread use of spirometric tests and specialist expertise;
3. to help patients self manage their own disease, through health education and pulmonary rehabilitation;
4. to integrate the care of patients affected by respiratory diseases, through linking specialist care to primary care, and extending end of life treatment from the oncological to the respiratory sphere.

In concrete terms, the specialist will build up a network in which the Operational Unit functions as the junction for the whole “vine” of respiratory care that begins with primary prevention and goes right through to palliative care, e.g. according to the following scheme of action:

- in *primary prevention*:
  - implement smoking cessation in prevention and treatment
  - increase the opportunity for screening for obstructive sleep apnea
- in *secondary prevention*:
  - increase accessibility to lung function assessment
  - experiment screening models for lung cancer
- in *improvement of patient management*:
  - expand and rationalize semi-intensive treatment
  - further reduce hospitalization through integration with services available in the local community, e.g. home hospitalization
  - monitoring of patients with chronic respiratory failure
  - health education
  - telemedicine
  - experiment a model of pulmonary rehabilitation provided in the local community
  - experiment the extension of palliative care to patients with severe respiratory failure.

#### Conclusions

Healthcare planning for respiratory diseases must undertake a whole re-think of its “mission” and a reorganization of the specialist network based on a redefinition of the role of the specialist. The goal is to achieve greater possibilities of self-management for the patient, greater responsabilization of primary care givers, through use of telemedicine, optimal crisis management, and greater options for dedicated and planned home care. The model for the hos-

pital pulmonary unit is similar to that of modern cardiology (i.e. intensive management of the acute crisis and of the immediate post-acute period in hospital) while that for the local community is akin to that of the services of diabetology (i.e. specialist consultation and guidance) with particular focus on self-management and pulmonary rehabilitation for patients with respiratory failure. The hospital specialist, who needs to be part of a Specialist Unit in order to have full knowledge of all the aspects, maintains the direct management of emergencies. For this the Pulmonology Unit must be an integral part of the critical area and not of the medical area, and its role in activities of non invasive respiratory intensive care needs to be recognized and promoted.

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## Long term oxygen therapy: a critical re-evaluation of current guidelines

### Ossigenoterapia a lungo termine: una rivalutazione critica delle linee guida attuali

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Oxygen therapy represents an essential part of treatment in the care of COPD patients with chronic respiratory failure. The evidence supporting the large

use of oxygen therapy and the current indications of international documents are based on the two landmark clinical trials (prospective and randomized) -

NOTT and MRC - published more than 25 years ago [1,2]. These studies showed that stable COPD patients, recruited according to pre-established inclusion criteria, live longer when they receive domiciliary long term oxygen therapy (LTOT) for more than 15 hours/day. The effectiveness of LTOT in improving survival has been documented only in COPD patients with severe chronic hypoxemia ( $\text{PaO}_2$  less than 55 mm Hg (7.3 kPa) or  $\text{PaO}_2$  ranging from 56 to 59 mmHg (7.4-7.8 kPa) in the presence of signs of cor pulmonale, hematocrit > 55%). The LTOT indications (based on NOTT and MRC) were established in a very selected and limited number of patients that are unlikely to represent the heterogeneity of the COPD population. These recommendations have been subsequently extended, albeit without solid evidence, to COPD patients with moderate hypoxemia ( $55 < \text{PaO}_2 < 65$  mmHg), and to patients with decreased oxygen saturation ( $\text{SaO}_2 < 90\%$ ) during exercise or sleep [3-7]. Increased life expectancy in the general population will lead into an increase in the numbers of patients surviving beyond age 70 with chronic diseases, like COPD. Comorbidities are very likely to affect both prognosis and health outcomes in COPD patients but clinical practice guidelines do not provide adequate guidance for patients in LTOT with complex chronic diseases.

It has been reported that reassessment of the indication for LTOT after some months of clinical stability reduced significantly the number of patients who would be eligible for LTOT soon after an episode of exacerbation [6]. The stability of underlying chronic disease before commencing LTOT is crucial. Actually, many COPD patients are prescribed oxygen therapy because they are hypoxemic at discharge from hospital after exacerbation of an underlying respiratory disease, despite an absence of data to support short- or long-term benefits of oxygen therapy. After acute exacerbations of COPD approximately 30-38% of patients improved  $\text{PaO}_2$  values merely by optimizing medical management to the extent that they no longer fulfilled the selection criteria for LTOT [8]. In order to optimize oxygen use it is advisable that patients should be reassessed, both at 3 months and at approximately one year after commencing oxygen therapy [9].

Furthermore, it is generally accepted without evidence that LTOT in clinical practice is warranted in other forms of chronic respiratory failure such as pulmonary fibrosis, kyphoscoliosis, and cystic fibrosis when arterial blood gas criteria are similar to

those established for COPD patients. Given the increasing numbers of patients receiving supplemental oxygen as treatment and the high costs incurred in providing oxygen therapy, a critical revision of the actual indications for LTOT is needed, particularly for COPD patients with comorbidities, mild-moderate hypoxemia, and exercise and sleep desaturation. Nevertheless, the high overall cost of LTOT is an argument in favour of prescribing it only for patients in whom there is a reasonable expectation of clinical benefit.

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## Lessons from large international clinical trials

### Le lezioni dei trial clinici internazionali

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COPD is a major cause of morbidity and mortality worldwide. Airflow obstruction is variable and results in hyperinflation, the hallmark of COPD physiological impairment. Besides the decline in lung function, COPD patients experience significant limitation in their daily life including dyspnea, exercise capacity, frequent exacerbations and hospitalizations. Long acting bronchodilators including  $\beta$ -agonists and anticholinergics with or without inhaled corticosteroids have been shown to impact these factors. Published studies over the last several years of pharmacotherapy have demonstrated improvements in lung function, dyspnea, decreases in exacerbations, improvements in health-related quality of life (HRQoL), and decreased mortality. Bronchodilators have also been associated with a reduction of dynamic hyperinflation, increased inspiratory capacity (by reducing the functional residual capacity), decreased work of breathing, improved ventilatory capacity and less dyspnea during activity and formal exercise testing. The long-term efficacy and safety of these medications were demonstrated in several multi-center, double-blind, 1-4 year long clinical trials.

Tiotropium, the first medication in the new class of long acting anticholinergics, exhibits a longer duration of action and has more specific muscarinic receptor antagonism. Its mode of action allows the medication to be given once a day, and further studies have shown that its half-life can be up to 36 hours. Clinical studies of long-acting bronchodilators, long-acting  $\beta$ -agonists (formoterol, salmeterol and recently indacaterol) and long-acting anti-muscarinic agents (tiotropium) showed significant improvement in trough, peak FEV<sub>1</sub> (range, 0.1-0.3 L) and average FEV<sub>1</sub> (range, 0.1-0.25 L) compared to a decline in placebo-treated patients (short-acting  $\beta$ -agonists, salmeterol and/or ipratropium).

Comparable results were achieved with FVC measurements. In order to compare the efficacy between these long-acting bronchodilators, Donohue et al. conducted a 6-month, placebo controlled, parallel group study of tiotropium vs. salmeterol in patients with COPD. Both active treatments resulted in significant improvement in trough, average (0 to 12 hours), and peak FEV<sub>1</sub> compared with placebo ( $p < 0.001$ ). At the end of 24 weeks however, trough, average, and peak FEV<sub>1</sub> improved significantly more with respect to placebo in the tiotropium group than in the salmeterol.

Clinical studies evaluated the use of combination of tiotropium and long acting  $\beta_2$  agonists showing that there is a synergistic effect of the combination ther-

apy and further improvement in lung function. This combination therapy will be suitable for patients with severe disease. The sustained improvement in lung function seen in these studies suggests that long active bronchodilators may slow the decrease in lung function over time and subsequently change the clinical course of the disease.

Furthermore, the impact of combination therapy (fluticasone propionate/salmeterol, and formoterol/budesonide) on patients' mortality, frequency of exacerbations and long-term effects on lung function has been reported. The TORCH (Towards a Revolution in COPD Health) trial is a large study that prospectively investigated the potential for combination therapy (fluticasone propionate/salmeterol) to impact survival in patients with COPD. TORCH was a three year, multicenter, randomized, double-blind, parallel group, placebo controlled study. Approximately 6,112 patients were randomized into 4 study groups: placebo, salmeterol, fluticasone propionate (500  $\mu$ g), and fluticasone propionate/salmeterol (500/50  $\mu$ g). The primary end point was the reduction in all-cause mortality, comparing fluticasone propionate/salmeterol with placebo. Secondary end points included COPD morbidity (rate of exacerbations) and quality of life assessment. The study showed a 17% relative reduction in mortality over three years for patients receiving fluticasone propionate/salmeterol as compared with placebo ( $p = 0.052$ ); a 25% reduction in exacerbations compared with placebo; and significant improvement in quality of life measured by the St. George's Respiratory Questionnaire (SGRQ). Taken together, existing data suggest that a fixed combination of long-acting  $\beta$ -agonists (LABA)/inhaled corticosteroid therapy has a significant impact in COPD by improving lung function, symptoms and HRQoL, as well as reducing exacerbations. Importantly, this therapy may also alter the course of the disease by reducing mortality.

The UPLIFT study results were recently reported. UPLIFT was a randomized, double-blind, placebo-controlled, parallel group trial designed to assess range of clinical parameters, including the rate of decline of lung function, quality of life, exacerbation frequency, rate of hospitalization and mortality in COPD patients (GOLD Stages II, III and IV) treated for 4 years with tiotropium 18 mcg inhalation capsule once daily. The study was conducted at 600 centers and involved over 6,000 patients. Findings showed that tiotropium compared with standard bronchodilator care resulted in a superior broncho-

dilator effect, less dyspnea, superior health scores, and fewer COPD exacerbations and hospitalizations. Tiotropium was also shown to be safe with significant less cardiac related events. Except for dry mouth incidence in tiotropium, adverse events were comparable with placebo. These data suggest that tiotropium has a significant role in COPD therapy. Clinical studies using triple therapy - tiotropium and fixed combination of long-acting bronchodilator and inhaled corticosteroid – have demonstrated an enhanced improvement in lung function, and reduction of exacerbations as compared with any product alone. Several of these studies also showed improvements in morning and daytime symptoms, nighttime awakenings, reliever use, and HRQoL. In COPD patients with severe and very severe disease triple therapy is highly effective.

Regardless of whether the treatment paradigm is driven by symptoms or spirometry, an important issue is whether regular treatment with long-acting bronchodilators and/or the combination of LABA-inhaled corticosteroids should be initiated at earlier stages of the disease. Recent reports of a sub-analysis of TORCH and UPLIFT studies show that patients with moderate disease will benefit from these therapies. These studies showed significant increase in trough FEV<sub>1</sub>, peak FEV<sub>1</sub>, dyspnea score, and HRQoL measured by the SGRQ. Notably, patients also have a significant reduction in exacerbations.

Roflumilast, an investigational selective phosphodiesterase 4 inhibitor, taken orally once daily targets the inflammation that is a hallmark of the disease. Participants in several 6- and 12-month studies who received roflumilast alone or in combination with salmeterol and/or tiotropium had a significant improvement in lung function, quality of life and reduction in exacerbations. Adverse events were mostly mild in nature. The two most frequent in the roflumilast group were diarrhea and weight loss. This medication is awaiting approval by the regulatory agencies.

In COPD patients, both airflow limitation and deconditioning lead to reduced exercise tolerance. Pulmonary rehabilitation (PR) has been shown to improve exercise tolerance, as well as dyspnea. A placebo-controlled trial tested the hypothesis that improvements in ventilatory mechanics resulting from tiotropium use would permit enhanced ability to train muscles of ambulation and, therefore, augment exercise tolerance benefits of PR. Tiotropium in combination with PR improved endurance in a constant work rate treadmill task and produced clinically meaningful improvements in dyspnea and health status compared with PR alone. Furthermore, following PR completion, improvements with tiotropium were sustained for 3 months. These data demonstrate that using long-acting bronchodilators will enhance the benefits of PR.

In conclusion, as the incidence of COPD increases, the need for agents that reduce associated morbidity and mortality is ever-growing. Long-acting bronchodilators alone and in combination with inhaled corticosteroids signify a major advancement in the

management of COPD. These medications have been shown to improve lung function, quality of life and exercise performance, decrease exacerbations, and reduce hospitalizations. Recent long term studies (3 to 4 years) showed sustained improvement in lung function, decreased mortality, and safety of these medications.

Several new long-acting bronchodilators are under investigation in clinical trials and will become available in the years to come.

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## Session II: Pharmaco-economics

### Sessione II: Farmacoeconomia

## The situation in North America: view from Canada

### La situazione in Canada

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The BOLD survey [1] estimated the prevalence of COPD in persons aged 40 years or older in Canada to be 11.1% (Stage I), 7.3% (Stage II) and 0.9% (Stage III-IV) or about 3.3 million. This is considerably higher than the official estimate of 750,000 Canadians with COPD that is based on reported physician diagnosis [2]. Clearly, as in other countries, there is a very large undiagnosed COPD population in Canada [3]. Despite this, respiratory diseases rank fourth in Canada in terms of the proportion of healthcare costs [2]. Hidden COPD in Canada is like a tsunami gaining strength, but which has yet to wreck on the shores of Canada's healthcare system, a system largely unprepared for the huge stresses that threaten to overwhelm our infrastructure, healthcare personnel, and financial resources. This in turn will prevent us from providing the comprehensive health care that these patients will need.

Healthcare in Canada is funded by each of our 10 provinces and 3 territories, with some additional federal funding transfers. Approximately 70% of

total healthcare expenditure is financed by government (provincial, territorial, federal) taxation [4]. All hospitalizations, physician visits and home care services are covered by the public purse. Patients do not have to pay for their assessments and there are no co-payment requirements, which allows Canadians to access a physician more easily than in many other countries. Primary care providers (PCP) are usually the first point of care for patients with COPD and the majority of physicians (PCPs and specialists) are paid on a fee-for-service basis according to the provincial fee schedule. Consultation by specialists, including 'respirologists' is generally arranged through a PCP, because services for non-referred patients are paid at a lower rate. The cost of delivering COPD care in Canada has been assessed [5-8]. The Canadian RUSIC study [5] estimated that acute exacerbations of COPD (AECOPD) requiring a medication change plus a visit to an outpatient facility including an emergency department had a mean cost of \$641 (CAN 2006 \$), whereas the mean cost of an AECOPD

requiring hospitalization was \$9,557. In 2003, data from the *Confronting COPD Survey* were used to estimate that the annual direct cost of COPD care including laboratory tests and visits to PCPs and specialists, was almost \$2000 per patient, with about half of the costs due to hospitalization [7]. The estimated economic burden of COPD through work loss was \$1,198 per patient, giving an annual societal cost of \$3,195 per patient. Costs increased in direct proportion to the severity of COPD as measured either by FEV<sub>1</sub> or MRC dyspnea score. Clearly, any therapy that will reduce the frequency of AECOPD, improve symptoms and slow down the age-related loss of FEV<sub>1</sub> in COPD should reduce associated healthcare costs over time.

There is no universal drug plan in Canada, and private payments are required for many citizens for medications, medical devices, some investigations and alternative practitioners such as chiropractors and optometrists. These payments are split between out-of-pocket expenses (15%), and private health insurance (12%), with the remaining 3% of payments provided by social services, charities and workmen's compensation benefits [4]. Provinces pay for medications for senior citizens (age 65 and over) and those on social services, but the medications provided come from a restricted list, which varies from province to province. This can be problematic in that the provincial drug formularies often favour generic versions of low cost drugs [9]. Thus while the Canadian [3] and other [10] clinical practice guidelines (CPG) for COPD recommend a long-acting anticholinergic bronchodilator or a LABA as first line treatment and combinations of long-acting bronchodilators (LABD) with or without inhaled corticosteroids (ICS) for more advanced disease, these restrictive provincial formularies act as barriers to physicians who wish to follow the CPGs.

For example, only 3 of 10 provinces fully funded tiotropium for COPD, while the remainder placed restrictions on its use, such as requiring that the physician provide spirometric documentation of advanced airflow obstruction and evidence of treatment failure on high dose ipratropium, before granting funding for the long-acting anticholinergic agent [9]. Similar restrictions exist for the combination LABA/ICS inhalers for COPD. A recent survey of Canadian PCP practice patterns in COPD in the provinces of Ontario and Quebec (CAGE study) observed that pharmacologic treatment that matched Canadian CPGs was present in only 34% of practices [11]. Non-prescription of LABDs for patients with moderate and severe COPD occurred in 27% and 21% of cases respectively and prescription of two LABDs for advanced COPD occurred only 49% of the time. A recent attempt [12] has been made to perform a cost effectiveness analysis of the Canadian [3] and GOLD [10] CPG COPD pharmacotherapy recommendations based on the results from the Canadian OPTIMAL trial [13]. This trial demonstrated that triple therapy with tiotropium plus fluticasone plus salmeterol (TFS) was superior to tiotropium plus salmeterol (TS), or to tiotropium

alone with respect to lung function, frequency of AECOPD requiring hospitalization and quality of life. The cost effectiveness analysis demonstrated that the incremental cost per exacerbation avoided with TFS was \$6,510 (CAN) and the incremental cost per quality adjusted life year (QUALY) gained was \$243,180 (CAN) [12]. Put in the context of what is considered an acceptable (to society) cost per QUALY gained and per AECOPD avoided, the authors of this analysis concluded that neither TFS nor TS were economically attractive alternatives compared with monotherapy with tiotropium for moderate-to-severe COPD [12].

It remains to be seen whether governments and third party payers will begin to consider requiring this type of cost effectiveness analysis when constructing lists of which drugs to support financially. Also yet to be considered is the price to society of increased longevity in COPD, such as that suggested recently in response to sustained bronchodilator therapy with expensive long-acting bronchodilators, with or without ICS [14-16].

Non-pharmacologic COPD therapies such as pulmonary rehabilitation (PR) have also undergone cost/benefit analysis in the Canadian context [6]. An economic analysis of a 2-month inpatient followed by 4-month outpatient PR program in Canada in 1997 estimated that it cost \$11,597 (CAN) to achieve clinically significant gains in dyspnea, emotional function, and mastery, with more than 90% of the costs being due to the inpatient phase of the program [6]. This data ignores potential cost savings resulting from fewer hospitalizations for COPD patients successfully completing a PR program [17]. It also emphasizes the value and potential cost-effectiveness of developing smaller outpatient and home-based PR programs [18].

A recent review has suggested that the most significant gains in COPD healthcare utilization have been realized by collaborative self-management education (SME) interventions [19]. A Canadian randomized controlled trial comparing case manager-driven SME versus usual care demonstrated a 40% reduction in the need for COPD patients to access healthcare resources including hospitalizations, emergency department visits and unscheduled clinic visits [20]. A cost-effectiveness analysis of this trial demonstrated significant net savings of \$2,148 (CAN) per patient, provided the case manager supervised 50 or more patients per year [8]. Canada is the first country to have certified respiratory educators (CRE), although many of these individuals are not fully employed. This reflects an under appreciation of the benefits of a collaborative self-management education approach to COPD care, which has led to under funding for such individuals. However, the situation is beginning to change as many provinces are moving towards a restructuring of primary care into multidisciplinary teams which are given financial incentives to provide comprehensive care including CRE-facilitated SME and whose physicians often forfeit fee-for-service remuneration in return for a salary and a less 'bottom line'-driven lifestyle [21].

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## The situation in North America: view from the United States

### La situazione negli USA

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COPD is a highly prevalent and morbid condition affecting 20-24 million United States citizens. COPD is the fourth leading cause of death in the U.S. with more than 125,000 deaths annually. In 2010, the direct health care costs of COPD are pro-

jected to total \$29.5 billion [1]. Of these costs, \$13.2 billion are hospital care costs, \$5.5 billion are physician costs, \$5.8 billion are outpatient prescription drug costs, \$1.3 billion are home health care costs, and \$3.7 billion are nursing home care.

Moreover, long-term oxygen therapy costs Medicare more than \$2 billion per year for COPD and the cost is growing by 12-18% per year [2]. In addition, there are \$20.4 billion in indirect costs due to lost productivity from death and disability. Lung volume reduction surgery and lung transplantation, although costly procedures, are infrequently used in COPD, so they do not presently account for substantial healthcare costs [3]. The primary goals of treating COPD are to improve functional status, reduce morbidity, and prolong survival. However, because substantial costs of COPD are related to health care use for exacerbations, it is a reasonable goal to consider therapy in terms of reduction in health care costs as well as direct expense for the drugs.

The current status of pharmacoeconomic evaluations of COPD has recently been critically reviewed and, while a number of methodologic flaws were found, the results were generally concordant [4]. Three older retrospective analyses have shown that the anticholinergic bronchodilator ipratropium in early stage COPD and a combination anticholinergic- $\beta$ -agonist in more advanced COPD are associated with lower overall healthcare costs, largely because of reduction in exacerbations requiring hospital care [5]. Another retrospective analysis compared costs of COPD treatment with ipratropium vs. theophylline [6]. Although the direct drug costs for ipratropium were greater, the overall healthcare costs were 28% lower in those patients treated with ipratropium, mainly because of reduction in exacerbations. An analysis of healthcare costs from a health maintenance organization database showed that monotherapy with ipratropium was associated with a reduction in healthcare costs compared to monotherapy with either a  $\beta$ -agonist, inhaled steroid, or theophylline in the first six months following a COPD diagnosis. Subsequent treatment with combination therapy with ipratropium and a  $\beta$ -agonist were also lower than other therapy groups [7]. These observational studies were supported by an economic analysis of two clinical trials of ipratropium-albuterol combination compared to ipratropium or albuterol alone [8]. Both of the ipratropium arms of the study indicated lower direct healthcare costs than albuterol alone. Again, the main component of the reduced expenditures was related to fewer exacerbations and fewer hospitalizations.

Long-acting  $\beta$ -agonists (LABA) as monotherapy for COPD are effective in reducing exacerbations compared to placebo, and a review of two clinical trials indicates that this translates into a reduction in healthcare expenditures, although these studies did not provide a comparison to other bronchodilator monotherapies [9]. Monotherapy with an inhaled corticosteroid, fluticasone, assessed in a placebo-controlled trial was found to be associated with a reduction in both direct healthcare expenditures as well as indirect healthcare costs from days of incapacitation [10]. A clinical trial comparing the long-acting anticholinergic tiotropium to ipratropium

demonstrated a 26% reduction in exacerbations and 46% reduction in hospitalizations associated with tiotropium. Calculations of costs using standard costs in The Netherlands indicated that the use of tiotropium, although more effective, was associated with increased healthcare costs for tiotropium due to the increased cost of drug acquisition. The cost-effectiveness of tiotropium vs. ipratropium is sensitive, however, to the relative costs of drug-acquisition compared to hospitalization and may have demonstrated a different effect on healthcare costs in the United States where the costs and charges for hospitalization are substantially higher than in The Netherlands [11]. This is further supported by a Spanish modeling study using outcome data from clinical trials comparing cost-effectiveness of monotherapy with salmeterol, ipratropium, and tiotropium. All three treatments were cost-effective in terms of clinical outcomes, but the most effective and highest cost monotherapy treatment was tiotropium [12]. Different strategies for initiation of inhaled corticosteroid therapy (ICS) in COPD were analyzed using a Markov chain model and using the assumption that ICS cause an initial increment in lung function but no change in the rate of subsequent decline. This analysis, which is highly dependent upon the assumptions regarding frequency of exacerbations and transition between different stages of COPD, suggested that the cost-effectiveness of ICS was greater in the most severely impaired individuals [13].

Three economic analyses of the TORCH trial have been published. TORCH compared salmeterol-fluticasone combinations (SFC) to the individual components and placebo. In one study using the United States cost structure, salmeterol was the most cost-effective drug (\$20,792/QALY) and SFC was second most cost-effective (\$33,865/QALY). Fluticasone alone, which did not improve survival in TORCH was not considered cost-effective [14]. A similar Markov-chain analysis of the TORCH trial, using different cost assumptions, found that SFC was the most cost-effective (\$52,046/QALY), followed by salmeterol monotherapy (\$56,519/QALY) and fluticasone monotherapy (\$56,519) [15]. In a third analysis of TORCH, using a multinational approach to cost structure, SFC was also found to be most cost effective with a cost of \$43,600 per QALY, compared to \$197,00 for salmeterol monotherapy and \$78,000 per QALY for fluticasone monotherapy. The cost-effectiveness was considerably lower for SFC in the United States (\$77,100/QALY) compared to Western Europe (\$24,200/QALY) [16]. Analysis of a Medicare HMO database using actual healthcare expenditures compared the costs of initial maintenance therapy for COPD using SFC, ipratropium monotherapy, ipratropium-albuterol monotherapy, and tiotropium. In this retrospective comparison, SFC was associated with slightly more cost savings than tiotropium (\$110/year), and ipratropium-albuterol (\$295/year), but substantially better than ipratropium alone (\$1235/year) [17].

In conclusion, a review of pharmacoeconomic

studies for COPD demonstrates that the analytic approach and baseline assumptions can lead to substantial differences in the conclusions that are reached. Nonetheless, there does appear to be substantial evidence that maintenance therapy in COPD is cost-effective and is comparable to the cost-effectiveness of treatments for other chronic diseases.

But the most effective therapies may exceed the threshold of willingness to pay by third-parties compared to management approaches in other chronic diseases. There are still substantial gaps in our knowledge of the comparative cost-effectiveness of other therapeutic strategies for COPD, particularly the combinations of therapies from different classes. In addition, we need to know better how the severity of COPD and clinical expression of the disease might influence the cost-effectiveness of comparative treatments.

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## The situation in Europe La situazione in Europa

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Obstructive lung diseases, particularly COPD are one of the main causes of morbidity and mortality in developed countries. In Spain, the prevalence of COPD was 9% in adults between 40 and 70 years

of age in 1999, although only 22% are diagnosed. In another population-based study performed ten years later, the observed prevalence was 10.2% and the underdiagnosis persisted, with only 27% of

TABLE I. COMPARISON OF THE COSTS PUBLISHED FOR COPD IN DIFFERENT COUNTRIES IN EUROPE

Reference	Country	Focus	Costs	Cost/patient/year	Global cost /year
Morera, 1992 [4]	Spain	Top-down	Direct and indirect	€959	Direct €319 M Indirect €541 M
Jacobson, 2000 [9]	Sweden	Top-down	Direct and indirect		Direct €109 M Indirect €541 M
Rutten van Mólken, 2000 [6]	Netherlands	Top-down	Direct	\$876	
Dal Negro, 2001 [10]	Italy	Bottom-up	Direct	Stage I = €151 Stage II = €3,001 Stage III = €3,912	
Jansson, 2002 [11]	Sweden	Bottom-up	Direct and indirect	\$1,284	\$871 M
Miravittles, 2003 [5]	Spain	Bottom-up	Direct	Stage I = €1,185 Stage II = €1,640 Stage III = €2,333	€427 M
Masa, 2004 [12]	Spain	Bottom-up Cross-sectional	Direct	€909.5	€238.8 M
Izquierdo, 2004 [13]	Spain	Bottom-up	Direct	Stage I = €1,657 Stage II = €2,425 Stage III = €3,303	
Borg, 2004 [14]	Sweden	Top-down	Direct and indirect	Direct costs GOLD I = €92 GOLD IIA = €631 GOLD IIB = €2,144 GOLD III = €8,678	
Detournay, 2004 [15]	France	Bottom-up	Direct and indirect	Direct costs GOLD II = €1,904 GOLD III = €2,683 GOLD IV = €6,357	€3,500 M
Lucioni, 2005 [16]	Italy	Bottom-up	Direct and indirect	Direct costs €4,645	
Koleva, 2007 [17]	Italy	Bottom-up	Direct costs	GOLD I = €1,046 GOLD II = €2,319 GOLD III = €3,572 GOLD IV = €5,033	
Dal Negro, 2008 [18]	Italy	Bottom-up	Direct costs	Mild = €1,314 Moderate-severe = €5,451	
De Miguel, 2008 [19]	Spain	Bottom-up	Direct costs	€1,922	

\$ = costs in U.S. dollars; M = million.

individuals with COPD having a previous diagnosis of the disease.

Considering its high prevalence and the chronic and progressive course of COPD, it is easy to understand that this disease will represent a high societal and economic burden. Studies performed in different European and American countries have tried to estimate the healthcare costs associated with the management of COPD patients. Costs obtained may differ in numbers, but in all cases they represent a significant proportion of the healthcare costs in each country.

Studies of costs of COPD have been performed in different countries and differ in their approach and methodology. In order to compare results among studies it is important to verify how the study has been designed. Basically, the differences derive from the inclusion or not of indirect costs. These refer to the morbidity and mortality caused by the

disease. They measure the impact which the disease studied may have on national production. The most common method of calculation is based on human capital in which days off work, whether because of disease or death, are transformed into monetary units by the application of the mean returns. This method has been extensively criticized, one of the reasons being that it does not include the impact on the collectives which are not integrated in the labor market such as children, the elderly, housewives, etc. In contrast, the direct costs are those related to the detection, treatment, prevention and rehabilitation of the disease studied. Most studies of this type concentrate on the analysis of the costs incurred by the hospital, ambulatory and pharmacologic care related to the disease in question. Other direct costs apart from health care, such as social services, are usually not included due to the lack of information. Another source of variation is the type of analysis.

One option would be to calculate the cost of disease starting with total figures at a national level for all the diseases together and, thereafter, reach the level at which the disease studied lies through a disaggregation process: this is called a top-down analysis. The second option would be to start by taking a group of subjects with the disease analyzed together as a base for the calculation and study the consumption of resources used during the time period considered. The national total may be determined by extrapolation of the costs of this subset of the population: this is called a bottom-up analysis. An example of the variation that can be observed in the calculation of costs is provided by the analysis of different studies in the same country, as in Spain. Top-down estimates have been carried out on the costs generated by COPD in Spain using statistical and epidemiological data. These studies have reported figures of around €800 million annually in 1994 including both direct and indirect costs. In a microeconomic study performed in 1,510 patients with ambulatory COPD followed over one year (bottom-up), the average annual cost per patient was \$1,876.00. With this study the approximate direct annual cost generated by COPD in Spain may be calculated from the focus of prevalence. If we take into account data obtained in the IBERPOC population-based epidemiological study, the prevalence of COPD was estimated to be 9% in the 40-69 year age group, of which only 22% were diagnosed and received treatment of some kind. Therefore, a total of 270,000 subjects would be diagnosed and treated for COPD multiplied by the annual average obtaining a total of \$506.52 million annually in direct health care costs generated by COPD. This figure is greater than that obtained with the previous focus which may be due to methodological differences and also, in part, to differences in the management of the disease during the period from 1994 to 1999 when information for the last study was collected. It is interesting to compare the distribution of the costs estimated in both models. In the top-down calculation the hospital costs constituted 36.3%, the expenses attributed to drugs 42.2% and the clinical consultations and diagnostic tests 22.5%. In the study using the bottom-up focus the hospital costs represented 43% of the total, drugs 40% and consultations and complementary tests 17%. Despite the differences observed in the absolute values between the two types of studies, the distribution of the costs was very similar. If the total direct cost of COPD is divided between the total of the country population, health care for COPD costs each citizen \$13.32 annually. To put this figure into perspective, a study carried out in The Netherlands reported a cost of \$23 per capita in the association of asthma and COPD. The differences may be due to the inclusion of asthma in the last study and a lower index of underdiagnosis in The Netherlands, among others. Other studies carried out regarding the cost of COPD in different European countries are shown in Table I. All estimates indicate that the situation will not

improve in the near future. The impact of aging and changes in smoking habits is responsible for an estimated increase of more than 60% of total life years loss and an increased loss of 75% of disability-adjusted life years (DALYs) from 1990 to 2020 in The Netherlands [20]. New projections performed until 2025 provide similar results with an increase in prevalence and costs of COPD despite the campaigns against tobacco smoking [21].

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## The situation in Europe: Scandinavia

### La situazione in Europa: Scandinavia

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The cost of pharmacological treatment is steadily increasing in all European countries. The main reasons are expensive, new hospital treatments with biological drugs and medications for cancer. The other main reason is that the population segment of elderly people is widening and with that the number of people with common chronic diseases including COPD. The cost of COPD in Denmark amounts to 10% of all health care costs.

The annual cost of pharmacological treatment in Scandinavia is today around €100 per inhabitant (from newborn to old age included). The cost in Denmark rose from about €2 billion in 2004 to €3 billion in 2008. This huge cost is mainly covered by the public health system, some private insurance and to a minor degree by the patients themselves. This immediately results in several interested parties involved in the actual use and choice of medication: i) health professionals (especially doctors and nurses as well as clinicians and clinical pharmacologists), ii) the patients and patient organizations, iii) the administrative systems with administrators, health economists and politicians, iv) the pharmaceutical industry, and v) public opinion with journalists and lobbyists.

A regulation by central guidelines, specific rules and norms seems justified. There are massive differences between regions in the prescribing pattern of drugs with the same effect and side effect profiles but in some cases a 10-fold difference in cost. Such unnecessary expense is obviously unwarranted because the treatment effect is the same for a less expensive drug. A 'correct' treatment can have an unacceptably high cost. Regional guidelines are therefore produced for the usual choice of a medication in a specific class of drugs (inhaled corticosteroid and bronchodilators, anti-TNF, ACE inhibitors, etc). These guidelines are publicized in

different ways and discussed with the health professionals. Other actions can be taken, e.g. withdrawal of the reimbursement from specific drugs, which makes the cost for the patient unacceptably high, or imposing rules such as disallowing renewal of the driver's license to elderly people treated with benzodiazepines. In special cases an audit and personal discussion with a doctor is arranged.

The general guidelines for handling a disease entity are usually formulated by the scientific society, and agreement about the general use of medication by classes based on a step wise approach according to severity is usually reached without problems among specialists. However, when it comes to the specific choice of a brand name, large differences in opinion often flare up. This may be caused by personal opinion about the effects of a specific medication and/or by a lack of interest in the economic aspect of drug use or the influence of the pharmaceutical industry. This is the background for the establishment of local pharmaceutical committees that explicitly choose labelled drugs in a prioritized sequence. This often occurs in the form of compromises between specialists with different opinions that have to find arguments for their choices.

A regulated practice has developed by law for pharmaceutical substitution in the pharmacy. This means that the pharmacy shall deliver another and cheaper medication to the patient than the one written on the prescription form, if the drugs contain the same active substance, in the same amount and are used in the same way. These are synonymous drugs and the practice is possible as the National Medical agency has made an evaluation. This means that the pharmacy gives the cheapest medication in almost all cases only with a few exceptions (allergy to constituents, the explicit wish of the patient or the prescriber for a certain drug, if the cost difference is trivial).

Diseases increase in incidence and prevalence with age, which makes the presence of comorbidities very frequent. COPD is a very good example of a disease with one or more comorbidities on account of age and smoking as a common risk factor (osteoporosis, cardiovascular diseases, cancer) and complications (depression and bronchiectasis). This is the reason why patients are treated with polypharmacy, that carries with it the risk of drug interactions. Patients with more than 5 drugs in their treatment should have their medication explained and reviewed for interactions.

Patients on inhaler treatment are all offered an evaluation of their inhaler technique and instruction in correct inhaler use, in order to improve the efficacy of inhaled medications and avoid waste due to ineffective inhaler technique.

Each country in Scandinavia has developed its own reimbursement system, that comprises a common part which applies to everybody and special rules for patients in specific circumstances. The common reimbursement scheme in Denmark is, roughly speaking, that the first €115 spent for the purchase of pharmaceutical drugs is not reimbursed (however, for age < 18 years, there is a 60% reimbursement also of this cost segment provided). The % reimbursement increases gradually to 85% with purchases above €400 in all age groups. However, per-

sons with chronic diseases pay up to a maximum of €450 out of their own pocket, and will have all additional cost covered. In special cases it is possible to apply for reimbursement of specific drug treatments, to have additional cost cover if the personal economic situation requires, or special support for terminal care and treatments.

A special group of people are the illegal immigrants, who have no public or private insurance. They experience serious problems when falling ill. They can in principle only be treated for acute severe disease and transported to their homeland as soon as possible, whereas management of the cost of chronic diseases is at their own total expense.

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## The situation in Italy

### La situazione in Italia

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In Italy, as well as in other industrialised countries, COPD still represents a major cause of morbidity and mortality, and exerts a substantial burden on health and the health care system. The "pharmacoeconomic era" started around the end of the last century and corresponded to the overall need for "accountability", and the economic evaluation of interventional strategies progressively became the crucial point aimed to support decision makers in allocating the ever diminishing health care resources. From 1979 to 2009, when compared to overall international and European studies, the Italian scientific literature in pharmacoeconomics of COPD gradually increased from 2.0% to 4.1%, and from 6.9 to 10.7% respectively. At present, while USA is producing the highest number of studies in this field (43.2%), Italy ranks 7<sup>th</sup> in the international seeding (3.4%), and 4<sup>th</sup> in Europe (8.1%), preceded by The Netherlands, UK and Spain.

In Italy, the cost-of-illness of COPD was calculated in 2002 for the first time: data were collected from 28 Lung Units, and the cost-of-illness analysis was carried out within the framework of the NHS [1]. Mean cost/patient/year ranged from €1,500 to 3,912 according to the illness severity, and direct costs (in particular, hospitalizations and ER admissions) represented the main driver of cost. Moreover, unacceptable levels for underdiagnosis and mistreatment of COPD were also confirmed in that study. In a further investigation [2], the mean societal cost of COPD was €1308/p/y: as 75% of cost was due to hospitalizations, a more effective strategy for managing and controlling COPD exacerbations was further strongly recommended in order to alleviate the burden of the disease in Italy. A few years later, the economic value of different therapeutic interventions (which were regarded as appropriate according to the most accepted guide-

lines) was investigated by means of a markovian model on the basis of their effectiveness in outcome optimization [3]. The key message emerging was that both a prompt diagnosis of disease and disease exacerbations, together with an appropriate and long-term therapeutic approach to COPD patients, represent the most effective strategy to optimize all outcomes related to the disease, and to substantially reduce the impact of COPD on patient, healthcare institutions and society as a whole.

Two years ago, health resources consumption and costs generated in 12 months by COPD were calculated on a national basis, in a real-life setting for a 1-year duration, and according to a bottom-up, observational, prospective multicentric study. At the end of the survey, outcomes were compared with those of the previous year [4]. A total of 748 patients were recruited, and 561 were defined as eligible by the Steering Committee; the proportion of moderate and severe COPD was 53.7 and 16.8%, respectively. Mean total cost/p/y was €2,723.7, ranging 913-5,452 according to the disease severity. At the end of the survey, requirement of health services had dropped significantly compared to baseline: GP visits by 57.4%; ER use by 12.5%; hospitalizations by 18.4%. Furthermore, even if direct costs remained the main driver of cost, the mean total cost per patient dropped by 21.7% ( $p < 0.002$ ), mainly due to a much more appropriate interventional and therapeutic strategy. When compared to previous studies, these data pinpointed that the mean total cost/p/y of COPD doubled in a 5-year period in Italy: this trend has also been registered in different countries (such as USA) over the same period. Quite similar figures were found in another study carried out on 268 COPD

patients from different lung units [5].

Data from a recent cross-sectional study carried out on COPD patients with different severity support the evidence that also moderate COPD represents a substantial economic burden for health care systems, and strongly indicate both the clinical and the economic convenience of an earlier, long-term therapeutic intervention in these circumstances [6]. To identify more incisive strategies for controlling COPD and minimizing related health care expenditure, cost-effectiveness and cost-utility models with a longer time-horizon should be adopted in future studies.

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## AGE.NA.S: national system for guidelines AGE.NA.S: il sistema nazionale per le linee guida

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The AGE.NA.S (National Agency for Regional Health Services) has, among its other activities, the responsibility at national level for the elaboration and dissemination of clinical and organizational guidelines. The strategic use of guidelines permits the evaluation of the quality of the services based on scientifically valid principles, recognizable by operators and decision makers. In fact guidelines constitute a primary source for the identification of indicators which can contribute in the assessment of appropriateness and they are a means of communication among professionals and of information to

citizens.

Guidelines have been criticized for how they rate the quality of evidence and the strength of recommendations, although with the development of systems such as GRADE - Grading of Recommendations Assessment, Development and Evaluation - this limit has been overcome. Concerns now remain about the necessity of elaborating ad-hoc initiatives for the correct implementation of guidelines at national and local (regional) level. For some clinical conditions limited information is available about current practice patterns and significant deviations

between current practice and guidelines regarding the use and selection of treatments have been found. Alongside this comes the razionalization of the use of health resources and the choice of diagnostic and therapeutic paths according to priorities which

should be established on the basis of the best available evidence. Therefore, in the development of guidelines efforts should be addressed to the examination and selection of interventions with a cost-effective profile.

## Session III: Inappropriateness at different steps of COPD management

### Sessione III: Inappropriatezza nei differenti passaggi della gestione della BPCO

## Prevention Prevenzione

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Reports estimate that, by the year 2020 COPD will have moved up, becoming the third leading cause of death worldwide. These astonishing statistics make it extremely important to identify risk factors associated with COPD and seek early treatment if symptoms arise. This is crucial as presently most people are not diagnosed until they are in their late 50s when a decline in their respiratory lung function has already set in [1].

Recognizing COPD risk factors and advocating lifestyle changes is the best way to maintain optimal respiratory health and prevent this devastating, life-threatening illness. Population-based and clinical studies have identified risk factors for COPD [2]. These can be divided into factors responsible for COPD exacerbations and factors responsible for COPD development. However, some factors are responsible for both the development and the exacerbations. Factors responsible for lung function impairment (which starts already during lung function growth), a main feature of COPD, have also to be taken into account.

Lifestyle modifications that can help prevent COPD, or improve lung function in COPD patients, include: quitting smoking, avoiding respiratory irritants and infections, avoiding allergens, maintaining good nutrition, drinking lots of fluids, avoiding excessively low or high temperatures and very high altitudes, maintaining proper weight, and exercising to increase muscle tone. However, data are insufficiently evidence-based for some factors.

Robust data exist, although to different extents, on active and secondhand tobacco smoke exposure, occupational exposure and outdoor and indoor air pollution [3]. Smoking is the leading cause of COPD. For instance, the American Lung

Association estimates that 80 to 90% of those diagnosed with COPD are chronic smokers. The amount an individual smokes as well as how long they have been smoking can increase the probability of developing the disease and intensify its severity. Risk factors are not only prevalent in those who smoke regular cigarettes, but exist for pipe and cigar smokers as well. Quitting smoking is the most important thing that one can do to prevent or slow damage to the lungs. Although it is not possible to undo the damage that smoking has already caused, further lung damage can be prevented by quitting. In terms of disease progression, other factors of COPD besides direct smoking that may also influence the course of the disease and its eventual health outcomes as well as the development, include secondhand smoke (SHS) exposure and occupational exposures [3]. Actually, an estimated 25-45% of patients with COPD have never smoked. The burden of non-smoking COPD is therefore much higher than previously believed.

Avoiding conditions that may irritate the lungs can reduce breathing problems in people with COPD. These conditions include indoor and outdoor air pollution; smog; cold, dry air; hot, humid air; or high altitudes.

SHS exposure is an important factor influencing disease severity and health status in COPD [4]. Previous studies suggest that SHS exposure may be a cause of new-onset COPD or impaired pulmonary function. The effect of SHS exposure on persons with established COPD, however, has received little attention. Because SHS is a modifiable risk factor, clinicians should assess SHS exposure in their COPD patients and counsel its avoidance. In public health terms, the effects of SHS exposure on the vul-

nerable subpopulations including COPD patients should provide a further rationale for laws prohibiting smoking in public.

Various studies have reported that exposure to toxic gases in the workplace, grain dust in farms, and dust and fumes in factories is strongly associated with COPD. In 2003, results of a systematic epidemiological review into occupational factors associated with COPD by the American Thoracic Society showed that about 15% of COPD cases might be attributable to workplace exposure [5]; and a subsequent follow up provided similar estimates [6]. Use of appropriate protective gear (e.g. face mask) in the workplace to avoid inhaling hazardous substances has also been documented as potentially relevant.

Exposure to indoor and outdoor air pollutants continues to be a major contributing factor to augmented morbidity, healthcare resources utilization and higher mortality among patients with COPD [7], particularly in the elderly [8], subsequently impacting public health, but there are few studies on whether air pollution is a key factor in the development of this disease. About 3 billion people, half the world's population, are exposed to smoke from biomass fuel compared with 1.01 billion people who smoke tobacco, which suggests that exposure to biomass smoke might be the biggest risk factor for COPD globally. Byproducts of oxidative stress found in air pollutants are common initiators or promoters of the damage produced in such chronic diseases. Such air pollutants include: ozone, sulfur oxides, carbon monoxide, nitrogen oxides, and particulate matter. Interaction between oxidative stress byproducts and certain genes may modulate the expression of COPD.

Strong evidence exists also for infections as a trigger of COPD exacerbations. Avoiding respiratory illnesses, such as influenza and pneumonia, can decrease the risk of COPD worsening [9]. Although clinical trial data are limited, vaccinations can prevent some of the infections that cause COPD exacerbations and should be administered to all patients with COPD. Vaccines do not cause exacerbations of COPD. Patient and physician barriers to vaccination have to be overcome with targeted education and system-wide interventions.

Lastly, physical activity has been shown to improve

lung health [10]. Airflow obstruction leads to progressive hyperinflation, activity limitation and physical deconditioning. Thus physical inactivity is an important therapeutic target in COPD. Targeting the airflow obstruction with therapy in conjunction with a supervised exercise prescription is currently the most effective therapeutic intervention in earlier COPD. Other important manifestations of skeletal muscle dysfunction include muscle atrophy and weakness. However, data on these physical effects are still scant.

The challenge we will all face in the next few years will be to obtain more robust data on risk factors for COPD development, progression and exacerbation and to implement cost-effective prevention and management strategies to stem the tide of this disease and its cost.

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# Diagnosis

## Diagnosi

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While the diagnosis of asthma requires symptoms, the diagnosis of COPD has often been based only on spirometry, given the presence of a provoking factor such as smoking or atmospheric pollution or occupational exposure [1]. Recently, the importance of adding medical history data to spirometry has been emphasized as there is still considerable underrepresentation and underdiagnosis of COPD and also as family physicians focus on presented symptoms. Thus, diagnostic guidelines should stress the importance of persistent cough and phlegm to support timely diagnosis of COPD in family practice [2].

Another important point is that the GOLD Committee suggested the use of a fixed FEV<sub>1</sub>/FVC cut-off of 0.70 instead of the more appropriate statistically defined lower limit of normal (LLN), claiming that the fixed ratio is easy to remember and to apply and not dependent on the choice of reference equation. Many recent papers have documented that the fixed cut-off of 0.70 significantly overestimates airflow obstruction in older people leading to misdirection of resources, unnecessary costs, and individual and societal harm [3-5]. On the other hand, it underestimates airflow obstruction among young adults leading to a missed opportunity for an early diagnosis of COPD in patients who are more likely to benefit from intervention [3]. Since diagnostic confusion between COPD and asthma appears common, bronchodilatation performed after spirometry may help to reduce the chance of misclassification.

The complexity and heterogeneity of the disorders encompassed by the term COPD with the overlap of different phenotypes have recently led to recommendations: i) that a new taxonomy is required to better define the disorders of airways obstruction and, consequently, ii) that clinical assessment should become increasingly multidimensional [6-

7]. Among lung function parameters, besides FEV<sub>1</sub>/FVC, lung volumes should always be included in the diagnosis of COPD as evaluation of hyperinflation is an important criterion in the phenotyping of COPD patients.

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# Treatment

## Trattamento

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It is generally accepted that COPD is not only preventable but also treatable. This change in concept from a previously nihilistic treatment paradigm based on smoking cessation being the only possible treatment for COPD has occurred over the last 2 decades as a consequence of several large trials including not only pharmacological agents but - equally important - pulmonary rehabilitation and even surgery (lung volume reduction surgery). It is inherent to these trials that patients be included only if they have COPD and by and large are free of concomitant morbidities that can impact negatively on the trial outcome, thus restricting the value of the results as the population is highly selected. On the other hand, once the results of the trials become available and, usually out of necessity, the findings permeate the larger community and patients get treated whether they meet the original inclusion and exclusion criteria or not.

It is in this stage of the implementation of therapies on a greater scale that treatments have to be monitored as to their safety and their likelihood to provide efficacy, thereby avoiding undue side effects and negative consequences.

In the specific case of COPD, the problem is compounded by the fact that these patients are frequently afflicted by multiple co-morbid problems. Heart disease, osteoporosis, peripheral muscle weakness and dysfunction, anemia, depression, anxiety and lung cancer are more frequent in patients with COPD than in the population at large. It is then imperative that safety be carefully determined in observational registries so that in the end a composite analysis of trial results is interpreted in the light of empirical usage. Following is an overview of the available evidence for the most frequently used treatments.

### Pharmacological treatments

Recently there has been concern that the long-term use of inhaled bronchodilators commonly used in the treatment of COPD, including long-acting  $\beta_2$ -agonist (LABA) and anticholinergic drugs, may increase the risk of cardiovascular complications. However, prospective data on the relative risk of therapy in patients with sufficient symptoms to be offered treatment with these drugs has, until recently, been lacking.

#### *Anticholinergics*

The safety profile of inhaled anticholinergics has been studied for many years. The short acting ipratropium bromide has been available to patients for over 20 years, and tiotropium since 2002. An asso-

ciation between ipratropium and cardiovascular mortality was noted in an earlier report from the Lung Health Study. However, a re-analysis of the same data by Lanes et al. showed that the increased risk of cardiovascular morbidity and mortality in that study was concentrated among patients who were randomized to the ipratropium group but who did not take ipratropium. Several reports have retrospectively examined safety data using different approaches with somewhat conflicting results regarding a possible association between inhaled anticholinergics, including tiotropium, and adverse cardiovascular consequences. In the first one, Lee et al. examined the association between various respiratory medications and risk for death in newly diagnosed COPD patients based on a retrospective nested case-control study using various databases. The authors concluded that ipratropium was associated with increased cardiovascular deaths, whereas inhaled corticosteroids were associated with reduced risk. The authors were limited by the data available to them, which did not include information on smoking or lung function. All-cause mortality risk ratio was 1.02 for ipratropium. The second analysis, by Singh et al., selected randomized controlled trials of any inhaled anticholinergic for treatment of COPD that had at least 30 days of treatment, and reported on cardiovascular events. The primary outcome was a composite of cardiovascular death, myocardial infarction, or stroke. The secondary outcome was all-cause mortality. While the report describes ipratropium and tiotropium trials both combined and separately, no differences in any cardiovascular effects would be expected between the two compounds based on their pharmacology. Singh et al. concluded that inhaled anticholinergics significantly increased the risk of the composite cardiovascular endpoint, myocardial infarction and cardiovascular death without a statistically significant increase in the risk of stroke. The analysis did not take into account differential discontinuation (i.e. in most of the trials, more patients in the placebo group prematurely discontinued the study than did patients taking active medication and were therefore followed for briefer periods of time during which adverse events were reported) and differences in exposure. The recent analysis of the large tiotropium database and the findings of the prospective UPLIFT study indicate a reduced risk for mortality from cardiovascular events and even overall mortality in patients receiving tiotropium. The mechanism by which tiotropium may reduce these events and improve survival cannot be precisely determined in the pooled clinical trial database but

an association with respiratory events must be considered given the significant reductions in exacerbations and hospitalizations observed. In the pooled analysis of 30 trials, tiotropium treatment also resulted in significant reductions in serious adverse events under the cardiac and respiratory organ systems. There are recognized limitations to pooling of clinical trial data. There are differences in populations, study design, duration of trials, collection of data and the ability to adjust for differences in exposure.

#### *β-agonists*

Like the antimuscarinic agents, β-agonists have the potential to precipitate cardiac rhythm disturbances and other cardiac events; however, this has not been regarded as important in clinical practice until recently. Unfortunately, unlike the situation for cardiovascular disease, most studies of drug treatment in COPD have been relatively brief (1 year and less) and have only reported on-treatment data. As the TORCH study was conducted in a patient group likely to be prescribed inhaled LABAs, that dataset addresses some of the problems inherent in these earlier analyses.

TORCH is the largest and longest prospective trial to examine the role of an inhaled LABA and an inhaled corticosteroid in COPD. Half of the over 6,000 patients were randomised to a regime containing SAL and, allowing for dropouts, this provided 7,231 patient-years of exposure to these agents. Over the 3 years, approximately 1 in 5 patients experienced a cardiovascular AE. The event rate was lowest in those receiving SAL in combination with FP, and not different from those patients treated with placebo or with LABA monotherapy. A SAE requiring hospitalization and new cardiovascular ischaemic events were approximately half as common as the total cardiovascular event rate, but there was a similar pattern across treatment groups. Seven percent of patients had a history of previous MI. In this group the cardiovascular event rate, as would be expected, was higher. Again, no trend was seen for more AEs in those patients randomised to treatment with SAL in combination with FP. However the data for SAL alone are inconclusive, possibly due to the small sample size in this smaller subgroup of patients.

Unlike other COPD studies, TORCH developed a rigorous methodology for determining the likely cause of death, which was adjudicated by an expert panel blinded to the study medication. Moreover, there was effectively complete follow up of the vital status of all patients 3 years after randomisation. The patients randomised to LABA alone had the lowest rate of cardiovascular death, while those who received placebo had the largest number of events. The number of on-treatment deaths, analogous to data included in earlier COPD studies, showed a similar pattern across treatments.

A range of predictable factors increase the cardiovascular event rate, including: greater age, a history of previous cardiac disease, and worse lung func-

tion. None of these factors interacted with treatment to identify a specific 'at risk' group.

#### *Inhaled corticosteroids*

If cardiovascular events are the most feared complications of patients receiving treatment with anticholinergics or β-agonists, the recent documentation that the risk of pneumonia is increased in patients receiving inhaled fluticasone has arisen from well controlled randomized trials. Based on the findings reported in the TORCH trial Ernst and colleagues reported the results of a nested case-control study within a cohort of nearly 176,000 patients with COPD that examined ICS use and the risk of hospitalization for pneumonia. Compared with non-ICS users within the past year, patients receiving at least 1,000 mcg/day of FP equivalent had a rate ratio for pneumonia hospitalization of 2.25 (95% CI 2.07– 2.44). In addition, the length of pneumonia hospitalization was similar whether or not patients were current users of ICS (mean 11.7 days vs. 11.8 days), as was all-cause mortality within 30 days of being hospitalized for pneumonia for patients dispensed ICS in the prior 2 months (8.2% of 18,005 patients) compared with those who were not dispensed ICS (7.4% of 5,937 patients). The careful review of all deaths reported in the large TORCH trial showed no difference in pneumonia mortality between patients receiving inhaled corticosteroids and those not receiving them.

What is very remarkable in the whole arena of pharmacological therapy is how much we have learned in the process. Medications have been shown to improve lung function, health status, decrease exacerbations and perhaps even impact on mortality but this has come at a price. Indeed, there is not only an economic cost but also the development of side effects that need careful monitoring over time. Fortunately, society has developed mechanisms by which the effect of drugs is monitored closely and even if not all problems can be prevented, it has made the agents available much safer to use.

#### **Non-pharmacological therapies**

The implementation of the National Emphysema Trial (NETT) was a first for the evaluation of surgical therapies. NETT represented the first surgical procedure subjected to a randomized trial using a medical comparator, in this case optimal medical therapy including pulmonary rehabilitation. Perhaps the greatest teaching to be derived from this study related to the initial report from the group. That publication dealt with the characterization of patients who had poor outcome when subjected to lung reduction surgery. Indeed, in the initial evaluation and follow up of the patients included in NETT, it became evident that a very low FEV<sub>1</sub> and diffusion capacity for carbon monoxide (DL<sub>CO</sub>) were associated with a very poor outcome. Indeed, these observations had important consequences for the field because they became reasons to exclude patients from consideration for lung volume reduction procedures. This report underscores the value of careful

assessment of new technologies, in this case for patients with COPD.

Perhaps a word of caution must be raised because alerting to the negative effects of a treatment prior to a full evaluation of the pros and cons of treatments may lead to premature killing of good ideas and therapies.

The last therapy that has generated great interest is that of pulmonary rehabilitation. Several modest size trials have been conducted but they have all emphasized the beneficial consequences of the therapy with very little information regarding bad outcomes or side effects. Perhaps, the most relevant information related to negative outcome is that of providing a picture of patients who do not want to participate in rehabilitation and, equally important, of how many do not complete the programs. The percentage of patients who do not join programs hovers around a very high 60% and out of those that join close to 30% fail to complete the program. Unfortunately very little has been done to better characterize those patients and evaluate the factors that lead to lack of compliance and uptake.

### Conclusions

Much has been learned about the inappropriateness of therapies through the implementation of the scientific method. Even though it may seem slow and complex, it is evident that application of these concepts in the area of treatment has enhanced our knowledge about the therapies that we provide to patients. As we enhance our armamentarium, it is important to remember that our current approach has served us well. We have indeed gained knowledge and confidence that the most frequently used therapies are safe and effective while we continue to investigate newer avenues to further empower our patients with a better future.

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## Follow up

### Follow up

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COPD is believed to become, in a few years, the third leading cause of death worldwide. Exacerbations of COPD are a frequent cause of emergency department visits and hospitalizations. An exacerbation of COPD is defined as a change in the patient's baseline dyspnea, cough, and sputum that is beyond day-to-day variations, is acute in onset, and may warrant a change in regular medication [1]. Exacerbations of COPD are common and present a major financial burden for most health care systems. The management of patients experiencing an acute exacerbation varies despite guideline-recommended care. Furthermore, there is little information on how to manage patients after hospitalization for COPD in order to optimize care and reduce the occurrence of a relapse [2]. Indeed, after an emergency department visit for an exacerbation of COPD there is a high probability that a new episode will occur in the first 2 weeks after discharge [3,4]. Exacerbations are not random events but the risk of recurrence is greatest within the first few weeks of the initial event [5].

Several risk factors have been identified that facilitate the occurrence of a new exacerbation, including: number of previous exacerbations, use of oxygen, lung function, absence of a primary caregiver and choice of pharmacological therapy [6,7]. For instance, patients who lack a primary caregiver use emergency care services more frequently than those who have a primary caregiver [8].

The lack of literature makes it impossible to provide specific recommendations for the management of patients after exacerbations of COPD. The use and value of spirometry, the potential benefit of home monitoring and of noninvasive ventilation as well as the value of long-term oxygen therapy, self-management programs and early rehabilitation need to be

better investigated. Current guidelines recommend a follow up at 4–6 weeks after hospitalization in order to assess clinical status, inhaler technique, the need for long-term oxygen therapy and FEV<sub>1</sub>. It is not clear whether a follow up earlier after discharge could reduce the exacerbation rate. There are few studies comparing the effect of a different frequency of follow up visits on the relapse rate of patients after hospitalization due to a COPD exacerbation. Available data suggest that an early rehabilitation intervention should be included in the follow up program. Rehabilitation is advisable after an acute exacerbation because it reduces the hospitalization rate and improves exercise capacity and quality of life [9].

In conclusion, although the current literature does not provide clear recommendations regarding all the components of a care plan following an exacerbation of COPD, a rehabilitation program should be included. Efforts should be made to improve the availability of rehabilitation for COPD patients in different health care settings.

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## Session IV: A new decade of COPD

### Sessione IV: Una nuova decade per la BPCO

## Pathogenesis of COPD: an innovative approach

### Patogenesi della BPCO: un approccio innovativo

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COPD is a severe multifactorial pulmonary disorder whose pathogenesis is not completely understood. Interestingly, a gradual shift from “inflammatory-based” pathogenic theories to more complex approaches has occurred in recent years [1]. Striking new evidence regarding the pathogenesis of COPD (in particular, emphysema) relates to its proposed inclusion within the category of diseases of “premature aging” of the lung, based on strong similarities with diseases characterized by telomere and stem cell dysfunction [2-4]. In the lungs, telomere erosion can variably affect the renewal potential of different stem cells, thus causing progressive depletion of relevant parenchymal components eventually culminating in alveolar loss and functional abnormality.

Interestingly, evidence is accumulating that also idiopathic interstitial pneumonia (IPF) can be included in the pathological category of diseases characterized by “telomere dysfunction” [5-7]. Tobacco smoke is a key pathogenic element in both COPD and IPF, and may serve as an environmental co-factor for the development of both diseases [5]. But how can this proposed similarity between the basic pathogenic mechanisms underlying COPD and IPF be reconciled with the obvious diversity of their pathologic and clinical presentations? The explanation could be sought in the heterogeneity of the underlying genetic alterations, as well as in the diversity of specific cell targets. Several reports in fact suggest that in IPF the major target is the alveolar epithelial stem cell (type II pneumocyte) [8] whereas in COPD mesenchymal cells (fibroblasts

and endothelial cells) within the alveolar parenchyma represent the Achille’s heel [9]. Thus, in COPD, abnormal apoptosis, senescence and loss of function mainly affect cells involved in the production of extracellular matrix proteins (elastin, fibronectin, etc.), with eventual weakening of the mesenchymal structure of the alveoli, leading to a defect in tissue reserve and “vanishing” of the supporting scaffold for epithelial cells.

Although some evidence has been provided of pneumocyte apoptosis, alveolar reparative mechanisms seem to be absent in emphysema, with no evidence of pneumocyte proliferation. The complexity of genetic predisposing features (e.g. telomere stricture together with alpha-1-antitrypsin deficiency, VEGF insufficiency, and/or others) working in concert with environmental factors may explain why mesenchymal progenitors are more profoundly affected in these patients. Accordingly, in emphysema tobacco smoke can severely affect mesenchymal function and repair, and senescence related markers are mainly demonstrable in fibroblasts and endothelial cells.

In conclusion, this evolving scenario opens up new possibilities for a better understanding of the pathogenic mechanisms of COPD and also IPF, and may yield new perspectives for alternative treatments of these devastating diseases acting on either pharmacological protection or specific replacement of affected stem cells [10].

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## COPD management: an integrated approach

### La gestione della BPCO: un approccio integrato

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#### A rapidly evolving scenario

Ageing of the population together with changes in lifestyle are central factors explaining the increasing prevalence of chronic disorders, which is expected to continue over the next decade leading to further dysfunctions of healthcare systems worldwide [1-3]. The urgent need to introduce substantial changes in the delivery of care for chronic patients is widely acknowledged. The World Health Organization (WHO) has launched the Innovative Care for Chronic Conditions (ICCC) initiative [4] formulating basic principles and strategies to enhance management of chronic patients [5,6].

There is evidence that information and communication technologies (ICT) can play an enabling role over the whole range of services, from life-style and self-management of health to improving health related quality of life of patients and citizens as well as managing chronic disease conditions [7]. Moreover, properly designed innovative health services supported by ICT might have a positive impact on chronic disease modulation and prognosis.

Despite the many advances and accepted potential of technology, ICT adoption in healthcare has lagged behind. The barriers originate at different levels and are associated to a multitude of technological, cultural, legal, and market related factors. Adoption of ICT in healthcare is currently a major

priority in Europe as shown by the major e-health deployment initiatives (e.g. epSOS) launched through the Competitiveness and Information framework Program (CIP) [8,9].

#### From management of crisis to integrated care

A recent analysis of the burden of all chronic conditions on tertiary care hospitalizations [10] indicated the need for revisiting managerial aspects of exacerbated chronic patients with a broad scope aimed at enhancing not only efficacy of care during the exacerbations, but also preventing admissions due to severe exacerbations in frail patients. In view of the high social and economic burden generated by hospitalization of patients with chronic disorders, new care modalities aimed at decreasing admissions through patients' empowerment and implementation of alternatives to conventional hospitalization have been developed in recent years [11-12]. It is of note, however, that a holistic approach of integrated care in chronic patients should not be focused only on prevention and/or management of crisis. Instead, principal targets should be early diagnosis and prevention together with future personalized care strategies launched at early stages aimed at modulation of disease progress and enhancement of prognosis. Successful strategies to address the current challenges impose

a progressive decline of the classical disease management approach towards new patient-oriented strategies including the adoption of a new health paradigm fitting the needs of chronic care, as proposed by the Chronic Care model [1-6].

Changes in lifestyle aimed at disease prevention and promotion of well being, empowerment of patients and relatives in self-management together with share care arrangements among the different levels of care are all necessary elements to improve efficiency of chronic care.

There is no doubt that current fragmentation among levels of care and community services constitutes a major limiting factor for a practical adoption of the principles formulated in the Chronic Care model. Moreover, management of comorbidity is a major challenge often overlooked by evidence-based diagnosis and treatment using disease-specific clinical guidelines.

Several disease-specific randomized controlled trials undertaken in patients with chronic heart failure, COPD, diabetes and other disease conditions have consistently shown the potential of integrated care to enhance clinical outcomes while generating cost-containment at system level. A common problem in all these pilot studies is that disease-specific trials have shown high internal validity but a questionable external validity because of an elevated rate of exclusion mainly due to severe comorbid conditions (~ 60% of cases) that could potentially be managed through transversal programs addressed to frail patients with multiple severe chronic disorders. The second most important exclusion factor, often present in frail patients, is lack of appropriate social support. As suggested above, there is a strong need to move the focus from the current interest in advanced chronic conditions toward the development of preventive integrated care strategies addressed to early stages of chronic diseases or even to citizens with high risk of developing chronic disorders. The ultimate aim should not be constrained to management aspects, but should be to achieve a positive modulation of the prognosis of chronic disorders. Note, however, that highly standardized interventions together with continuous evaluation of results will be required.

In order to face all these challenges, more and more attention is being paid to the evolution of health systems from a provider-centered perspective to a patient-focused approach. In the integrated care scenario being deployed in the NEXES "Living healthily at home" project, chronic patients included in well standardized care programs are managed through a support center (multimedia call center) to enhance accessibility to the specific type of care needed (Figure 1). Major organizational adjustments of health systems combined with significant educational changes are urgently needed in order to prepare the healthcare professionals for new and evolving roles. Moreover, there needs to be a major adjustment of financial modalities for the services to ensure sustainability of integrated care supported by ICT.

### Extensive deployment of integrated care service

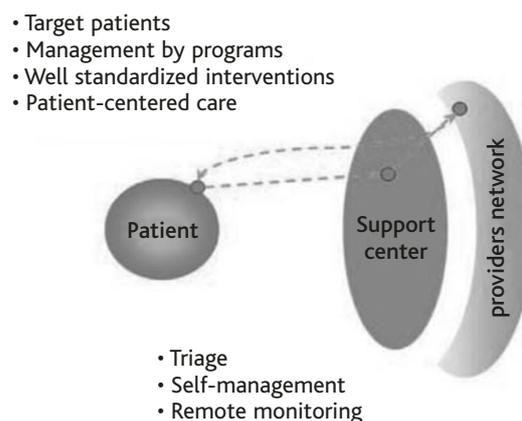
NEXES is the acronym of the project "Supporting Healthier and Independent Living for Chronic Patients and Elderly" conceived to face the transitional phase from existing pilot experiences to deployment of health/social services targeting selected groups of patients. It supplements and/or represents an alternative to existent conventional approaches. The project grew from the need to unfold previous pilot experiences on innovative healthcare services supported by ICT, already mentioned above. The main objective is to evaluate the potential for generalization of four specific services (see below) targeting citizens at risk and patients with chronic illnesses. NEXES will mainly address patients with one or more of the following chronic conditions: COPD, chronic heart failure and diabetes type II.

In this scenario, ICT plays a fundamental support role in the new health model. The services to be validated through randomized controlled trials will be carried out in large scale studies including approximately 5,000 patients. The four types of services indicated below cover the needs of a broad spectrum of health problems, from those affecting citizens at risk or with early disease to those addressing frail patients with advanced chronic disorders.

- 1) Wellness and rehabilitation aimed at promoting healthy lifestyles in clinically stable chronic patients and enhancing their self-management
- 2) Enhanced care for frail patients to prevent unplanned hospitalizations
- 3) Home hospitalization of chronic patients with severe exacerbations aimed at optimization of home hospitalization
- 4) Support to diagnosis and/or to therapeutic procedures including collaborative tools for professionals working at different healthcare levels to enhance their potential for action in home-based interventions.

All services will be assessed at three distinct sites

FIGURE 1: INTEGRATED CARE SERVICES AS DEPLOYED IN THE NEXES PROJECT



(Barcelona, Central Norway Region and Athens) notwithstanding some existing differences in the specifics of healthcare organization. The impact of heterogeneities among sites will be evaluated. The differences among sites may offer opportunities for planning of co-developments at cross-border level in the deployment phase. One of the primary objectives of NEXES is to provide robust results to health technology assessment agencies and to decision makers in order to facilitate the extensive deployment of the services and the sustainability of the care model.

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## A comprehensive approach to COPD Un approccio onnicomprensivo alla BPCO

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COPD is a multicomponent disease with inflammation at its core, in which patients experience progressively worsening lung function, disease symptoms and quality of life, as well as increasing exacerbations. The therapeutic challenge presented by COPD arises from the need to target all components of the disease. In recent years a number of large clinical trials have been carried out aimed at answering major questions on the long-term management of COPD.

These clinical studies have been mainly addressed to clarify the following open questions:

- what is the best maintenance therapy from GOLD III to IV treatment?
- is earlier intervention important for COPD treatment?
- do bronchodilators have an impact on COPD mortality?

COPD is a treatable disease and the long-acting inhaled medications for bronchodilation in COPD include long-acting anticholinergics and long-acting  $\beta_2$ -agonists. Each has shown to improve FEV<sub>1</sub> by a mean of approximately 150–250 ml more than

placebo. These agents also significantly improve health-related quality of life. Meta-analyses have demonstrated that these long-acting inhaled medications are associated with significant reductions (20–26% per year) of acute exacerbations of COPD. In addition to pharmacological therapy, patients with moderate to very severe COPD have been shown to benefit (improved health status, quality of life, and exercise tolerance) from participation in a pulmonary rehabilitation program. In COPD patients with chronic, resting hypoxemia, use of supplemental oxygen for > 15–18 hours per day has been shown to improve mortality.

Finally, very severe COPD patients may benefit from lung volume reduction surgery, which improves health-related quality of life and exercise tolerance in patients with FEV<sub>1</sub> < 30% predicted and mortality in carefully selected patients with upper lobe bullae and low exercise capacity. Lung transplantation is another potential option for COPD patients without significant comorbidities but with extremely limited functional status, to improve quality of life (QoL).

COPD is a reversible disease if patients receive appropriate therapy. The reversibility relates to exercise capacity and QoL. High on the list of specific complaints that contribute to poor QoL in COPD patients is intolerance concerning everyday activities (due to abnormalities in lung mechanics and gas exchange, and to dysfunction of the ambulation muscles). Bronchodilator therapy and supplemental oxygen have been shown to improve exercise tolerance in the COPD patient and pulmonary rehabilitation is acknowledged to be the most successful intervention for improving exercise capacity.

A recently published evidence-based analysis concluded that the highest grade of evidence supports the inclusion of endurance and strength training as well as upper extremity exercise and that rehabilitation programs reduce dyspnea and improve QoL. Current research is seeking to find ways to increase the duration of benefit of pulmonary rehabilitation and to determine whether rehabilitation imparts a survival benefit.

Another important issue is the role played by early intervention. In fact COPD in its early stages (stages I and II) is usually not recognized, diagnosed or treated, and therefore it may not be included as a diagnosis in a patient's medical record. Earlier intervention therefore refers to early recognition, diagnosing, and treating of all COPD patients requiring management (i.e. treatment) according to international recommendations. Why intervene earlier? Because significant lung damage may exist even in "early" disease, as defined by lung function, when patients may be 'impaired' but deny or under-perceive their symptoms and functional impairment. Treatment can be shown to improve function in patients when disease is at an earlier stage and it can impact the clinical course of COPD.

About the impact of bronchodilators on COPD mortality, the TORCH study showed a reduction in death from all causes among patients with COPD in the combination therapy group, though this did not reach the predetermined level of statistical significance. The UPLIFT study showed that tiotropium improves the natural history of COPD patients reducing mortality by approximately 11-16% and FEV<sub>1</sub> decline in GOLD stage II patients.

In conclusion, the experience emerging from large clinical trials carried out in recent years in over 40,000 COPD patients per year/experience indicates a sustained improvement in lung function, quality of life, exercise capacity, decreased frequency of exacerbations and mortality through the long term use of bronchodilators. In addition to these data we have further evidence that long acting bronchodilators should be used in patients with moderate (GOLD II) disease, improving lung function and impacting the clinical course of the disease.

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