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An epidemiological overview and clinical picture of COPD in the elderly

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Chronic Obstructive Pulmonary Disease (COPD) is a primary cause of disability and death in the elderly. Its prevalence is dramatically rising, mainly among females, but reliable figures are not available because many elderly, mostly the ones plagued with disability and multimorbidity, cannot perform a good quality spirometry, a sine qua non diagnostic tool. Furthermore, atypical presentations contribute to conceal COPD. Even in patients who received a standardized diagnosis of COPD the GOLD recommended staging criteria are questionable because of some imbalance between classificatory and prognostic properties. The great variety of symptoms applies to both stable and exacerbated COPD. Thus, to diagnose an exacerbation timely may be difficult if the individual pattern of symptoms has not been previously recognized. Accordingly, a truly comprehensive assessment is mandatory to clarify the unique clinical pattern of a given patient and, then, to tailor the multidimensional therapeutic strategy. Such an approach largely depends upon the specialty of the physician in care. Thus, efforts are needed to make all the specialists caring for the elderly respiratory patients share the cultural and procedural patrimony allowing recognize and optimally care these "difficult" patients.

Key words: COPD, Elderly, Disability

AN EPIDEMIOLOGICAL PERSPECTIVE

COPD, a chronic non communicable age-related condition, is primarily related to smoke. This explains its higher prevalence among males, but also the ongoing epidemiologic changes driven by the spreading of smoke addiction among females [1]. However, at least one out of four or five people with COPD denies a history of smoking [2]. Indeed, environmental factors contribute to the pathogenesis of COPD. Among these, pollution, mainly at working place for males and at home for women living in less developed countries, plays a primary role. Other highly prevalent risk factors for COPD are recurrent pulmonary infections and malnutrition [2]. Age qualifies as a "summary" risk factor because it directly reflects the cumulative exposure to the recognized risk factors. This underlies the link between older age and COPD and makes COPD a primarily geriatric condition. This also explains the clustering of COPD with other chronic diseases sharing the same or a very similar profile of risk, i. e. the place of COPD in the multimorbidity framework [3].

Despite this solid epidemiological evidence, the true prevalence of COPD among the elderly remains uncertain. A 9% prevalence has been estimated in the general population in the 2000-2007 period, but much higher figures are known to characterize the elderly [4]. For example, in the Norwegian Hordaland County Cohort Study, the prevalence of COPD in people aged 65 and over was 28% *vs* 14% in the 50-64 years cohort in the 2003-05 period and 20% in the same cohort over 64 in the 1996-7 survey [5]. In Lazio, the prevalence in males dramatically rises with age from 7% in the 60-65 year cohort to 24% in the 80-85 year cohort; the corresponding figures for females are 8% and 17% (Fig. 1).

The high rate of underdiagnosis is especially due to the very stringent diagnostic criteria requiring a high quality spirometry for a diagnosis of COPD to be made [6]. Indeed, in the SaRA study it has been proved that 836/1971% of people over 64 years of age attending the outpatient clinics of Geriatrics or Respiratory Medicine of 20 Italian hospitals were unable to perform spirometry or could

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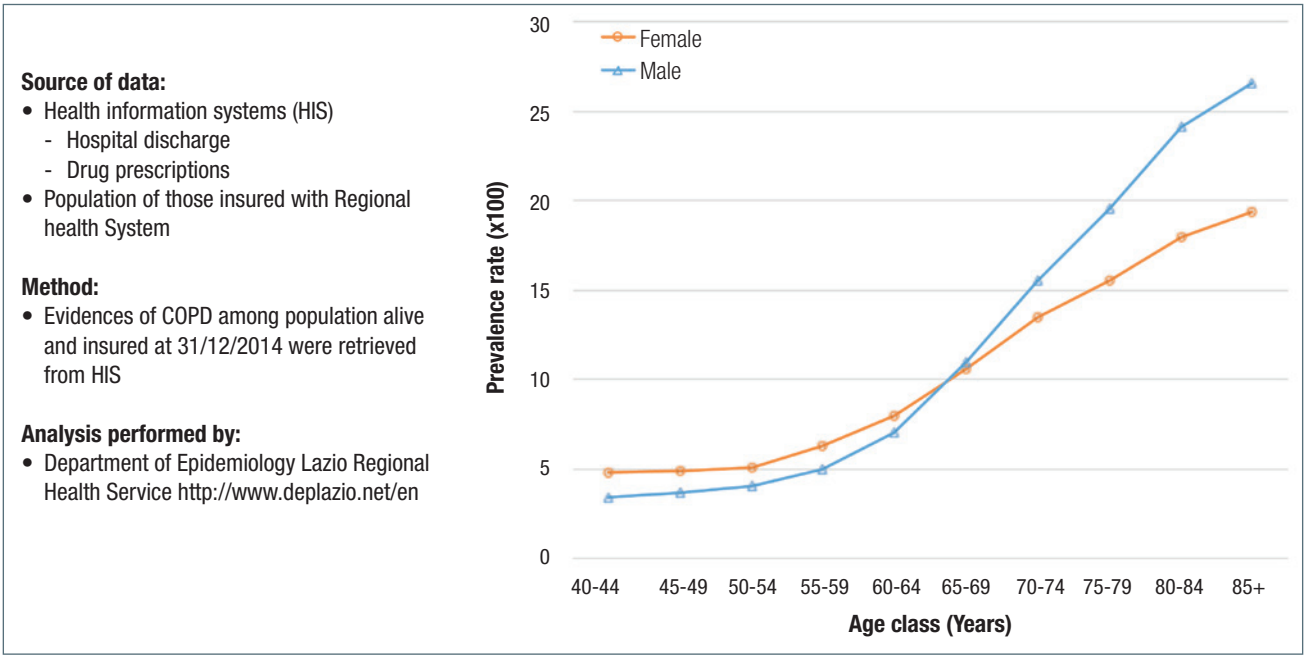


Figure 1. COPD age-specific prevalence rate at 31/12/2014 Lazio Region, Italy.

not meet the acceptability or repeatability standards of spirometry and, then, could not receive a diagnosis of COPD [7]. This fraction fell to 702/1971% if the FEV6 was used as a surrogate of FVC [8]. However, FEV6 is not routinely used for people unable to produce a canonical FVC and, in any case, even for FEV6 the proportion of non achievers is unacceptably high. Risk factors for a poor quality spirometry are cognitive impairment, disability, polyharmacy, poor education and older age [7]. As a consequence, the most compromised patients are also those most likely to remain unrecognized and untreated. Furthermore, the randomized pharmacological clinical trials exclude these patients: only one out of five enrollees in a RCT is representative of the elderly people attending an ambulatory of Respiratory Medicine [9]. Thus, a double bias affects elderly people with COPD: a diagnostic bias and a therapeutic one given that the available evidence on the therapy of COPD stems from RCT excluding these patients. Broadly speaking, COPD is typically underdiagnosed at any age with the fraction of concealed cases ranging between 63% and 82% depending upon the setting and the method [10]. The high rate of missing also in adult and even young-adult people testifies to a lack of attention to and, more in depth, poor awareness of this disease. The problematic and frequently elusive clinical presentation partly justifies this finding. Misrecognition becomes more and more important as people age because of age-related and comorbidity-related changes in symptoms and non respiratory confounders.

THE MISLEADING SYMPTOMS

The difficulty to recognize COPD to some extent reflects the variability of the symptoms with the phenotype of COPD as well as longitudinally in the same patient. Furthermore, the chronobiology of symptoms changes from patient to patient as also highly variable is the presentation of COPD exacerbations. Finally, comorbidity and disability contribute to make symptoms a true puzzle.

A) Relationship between symptoms and phenotype: two extreme phenotypes, the bronchitic one and the emphysematous, traditionally mark the extremes of the phenotype range. A variety of other phenotypes, e. g. the asthma-like and the Combined Pulmonary lower lobe Fibrosis and upper lobe Emphysema [11], coexists. The bronchitic phenotype is easier to recognize, whereas the emphysematous phenotype may be missed in the elderly for many reason. First, the patient adjusts to the reduced respiratory reserve by decreasing her/his physical activity, thus preventing the onset of dyspnea and having a sort of downsized life. Interestingly, the misconception that age itself necessarily curtails our range of physical independence frequently founds this coping strategy. Also the bronchitic phenotype may be the object of misinterpretation. For instance, bronchiectases are frequently missed as comorbid or else main disease, and the missing is clinically important because physical therapy and selected

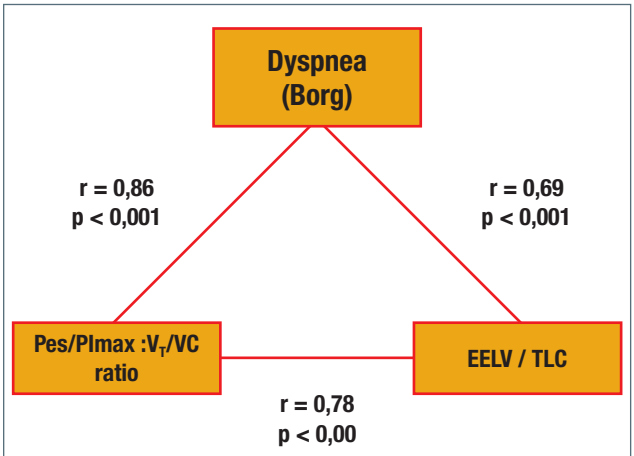
pharmacological measures have the potential for improving the health status of these patients. The epidemiology supports the link between bronchiectasis and COPD: COPD was the most common secondary diagnosis (39,8%) when bronchiectases were the main discharge diagnosis [12].

B) Chronobiology of symptoms: a notable contributor to the clinical phenotype, the circadian rhythm of symptoms would deserve much more attention than currently paid to. Indeed, distinctive clusters of symptoms have been reported and contribute to shape a clinical phenotype. For instance, nocturnal symptoms have been reported in about 60% of COPD patients [13], and wheezing is the most common among these [14]. However, it is unknown whether this reflects a true asthma-like feature or to some extent an unrecognized left ventricular dysfunction underlying cardiac asthma. Furthermore, coughing and not wheezing has been rated as the most common nocturnal symptom in the recently released Assess study [13]. Insomnia is also highly prevalent in elderly COPD patients and its prevalence increases for increasing age from 65 to over 90 years, whereas such an increase is not evident in patients with chronic non respiratory diseases [15]. Finally chest tightness, a symptom suggesting coronary artery disease, has been reported by about one out of four COPD patients [16].

C) Frequency and clinical presentation of the exacerbations: in the last five years a trend is emerging towards recognizing a new phenotype, the "frequent exacerbator", based exclusively on the yearly number of exacerbations. Having two or more exacerbations would define such a new phenotype irrespective of which are dominant symptoms. Supporting this view is the finding of a stable number of exacerbations during the natural history of the disease in the individual patient starting from the earliest stages of COPD, also if some increase in frequency marks the passage to higher stages of the disease [17]. The current evidence is insufficient to confirm the existence of such an hypothetical phenotype. Indeed, in people over 75 years frequency of exacerbations is inversely related to the income, and the same is true of other chronic non respiratory conditions [18]. Thus, it is likely that the social dimension and not a biological one underlies the frequency of the exacerbations.

   The clinical pattern of the exacerbation dramatically changes from patient to patient. In a series of 80 consecutive people attending an emergency room for exacerbated COPD, leg oedema secondary to severe hypoxia and hypercapnia, chest tightness simulating a cardiac attack, dizziness and postural instability due to hypoxemia and fatigue were the prevailing symptoms in about 20% of patients, while dyspnea was the hallmark of typical presentation. Interestingly, patients with "atypical" presentations of the exacerbation frequently had a correct diagnosis not in the emergency room, but in the hospital ward 24-48 hours later [19]. Further complicating this issue is the fact that the percutaneous measurement of Oxygen saturation is frequently unreliable in the elderly and multimorbid patient due to one or more of the following factors: atrial fibrillation and other arrhythmias, venous congestion, low blood pressure, cold skin, anemia, shivering patient, movements, bright light [20]. The remote multiparametric monitoring of elderly COPD patients allowed know different onsets of the exacerbation with selected and clinically problematic patterns such as progressive decrease in physical activity, a sort of downtailoring of the range of activity in response to worsening COPD, or increased respiratory rate without any other symptom or sign for a while [21].

D) Impact of comorbidity and disability on symptoms: disability frequently limits the physical activity and, then, prevents the patient from reaching the threshold of dyspnea. Accordingly, alternative symptoms such as fatigue, dizziness, non specific malaise, defective attention and concentration may dominate the clinical scenario. This results in a seemingly and, thus, potentially misleading "non respiratory" pattern of symptoms. Analogously, selected comorbid diseases may act as clinical confounder. This is the case of coronary heart disease, congestive heart failure, obstructive sleep apnea syndrome and some others. Indeed, the differential diagnosis between cardiac and respiratory dyspnea, between cardiac and respiratory chest tightness and between COPD- and OSAS-related symptoms may be difficult. Furthermore, the comorbid disease itself may change in clinical presentation as a function of age. This is the case, for instance, of OSAS: in the elderly the classical pickwikian phenotype is the exception and not the rule, and both snoring and day time somnolence are not more prevalent than in non OSAS elderly people, whereas subtle cognitive dysfunction and nicturia, which is commonly ascribed to urologic problems, are distinctive clinical features [22]. All these problems make the diagnosis of COPD in the old and multimorbid patient, i. e. in the real life patient, the end result of a hard attempt at disentangling and interpreting several and frequently atypical, at least with regard to adult based knowledge, symptoms (Fig. 2).



Legend: Dyspnea largely depends upon a complex dynamic interplay between diaphragm effort (Pes/PImax:VT/VC, where Pes= esophageal pressure, Pimax= maximal inspiratory pressure; Vt= tidal volume; VC= Vital Capacity) and pulmonary hyperinflation (EELV/TLC= End Expiratry Lung volume/Total Lung Capacity). Instead, FEV1, reflecting bronchial obstruction, accounts only for 20% of the explained variance in the Medical Research Council scale of Dyspnea (Perez et al. Prevalence of chronic obstructive pulmonary disease in asymptomatic smokers, Int J Chron Obstruct Pulmon Dis 2015).

Figure 2. Inter-relationships at a standardized level of exercise (from O'Donnell et al.,1997 [23] and Perez et al., 2015 [24], mod.).

SOME NOTES ABOUT COPD STAGING

The staging of COPD was based only upon the degree of bronchial obstruction, as expressed by the FE1/FVC ratio, until 2009. With the 2009 update of GOLD guidelines a new classificatory system has been adopted and is currently recommended. This system has merit in that it takes into account the clinical disease severity as expressed by dyspnea, health status and frequency of exacerbations. However, respiratory function remains a necessary diagnostic criterium. The whole classificatory system is to some extent cumbersome as it requires a careful diagnostic procedure. Furthermore, it is intended for the pure COPD patient or, at least, for patients having COPD as the main determinant of health status. This does not occur in the majority of the elderly patients, else the main disease frequently changes with the time.

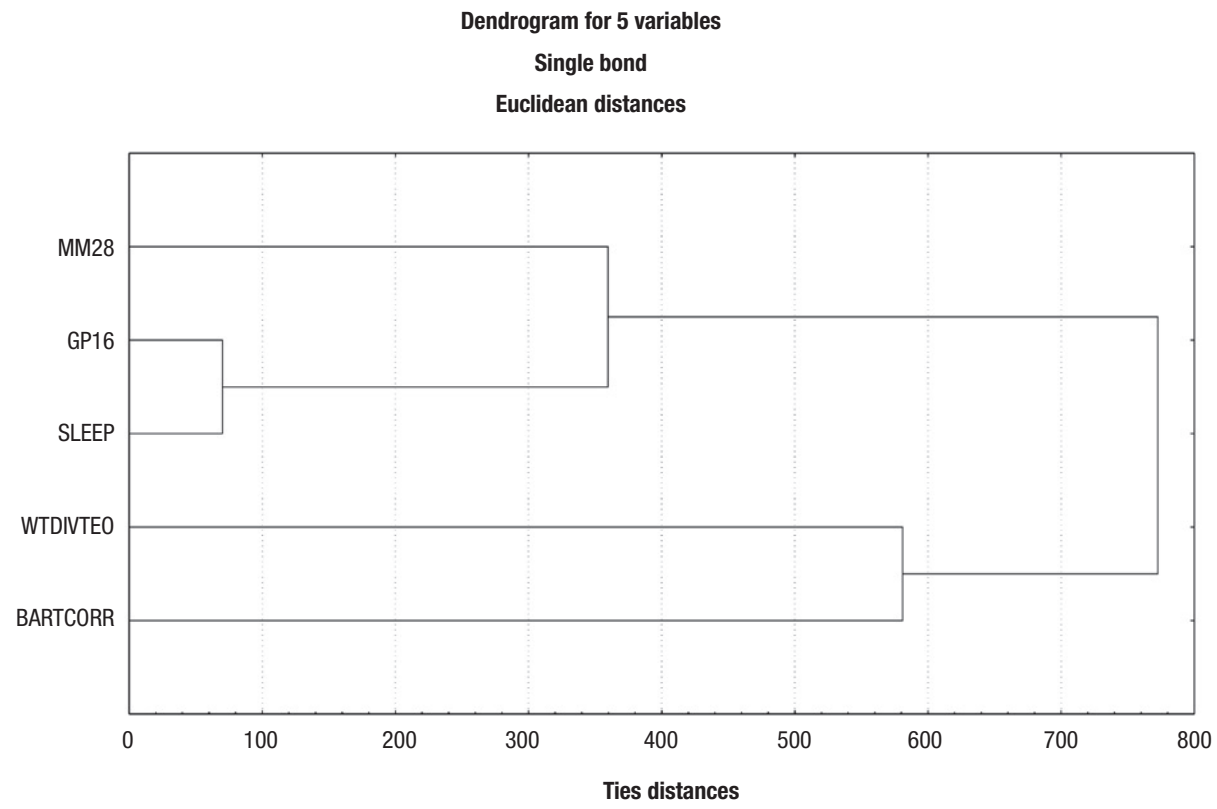
A practical application of the GOLD classificatory criteria will clarify this issue: a patient with GOLD class 2 obstruction (FEV1/FVC < 70%, FEV1 = 50-80% predicted), MRC = 1 and CAT = 8 will be classified as in stage A or B GOLD depending upon whether she/he had 1 or more than one exacerbation in the previous year. It is evident that this last criterium is problematic in the elderly and multimorbid patient who experiences many episodes of worsening health status during one year and frequently has trouble to recognize their respiratory origin. Furthermore, the epidemiological evidence is consistent with GOLD stages having poor prognostic capacity: in the Norwegian Nord-Trøndelag Health Study 1995-1997 survival did not distinguish A from B and C from D patients [25]. It should also be recognized that MRC score may be misleading due to the variable coping strategy used by the old patient (see previous section).

The methodological and procedural problems reported in this and in the previous section point at the need of an alternative approach to the elderly patient with a clinically founded suspect of COPD if a spirometry is lacking. In these patients the ex juvantibus criterium may be the only way of testing the suspect of COPD: an improvement in measurable outcomes such as symptoms and physical performance after the start of topical bronchodilators may be the key to a putative diagnosis of COPD as well as the only means of improving health status.

In the near future the analysis of the breath pattern through highly innovative technique like the electronic nose might allow recognize distinctive metabolic patterns marking COPD and distinguishing it from other chronic diseases. Preliminary results are highly favorable [26]. If confirmed in larger population, these findings will pave the way to an easy diagnosis of COPD and, thus, will remove the exclusion of the frail and multimorbid patient from the standardized diagnostic and therapeutic pathways.

RELATIONSHIP BETWEEN DISEASE SEVERITY AND HEALTH STATUS

On average, health status worsens for decreasing FEV1, but the decline becomes dramatic for FEV1 < 50% [27]. However, in the broad population of elderly COPD patients, the bronchial obstruction is weakly correlated with health status, at least in patients with mild to moderate obstruction. This finding reflects the multifactorial origin of health status impairment in these patients. Indeed, dyspnea, the main threat to personal independece and well being, largely depends upon factors which may be only barely reflected by bronchial obstruction (Fig. 3). Among these are dynamic hyperinflation, respiratory muscle fatigue and neurologic and psychologic factors such as the coping strategy. Furthermore, limitation of personal capabilites is variably determined by sarcopenia and fatigue of peripheral muscles, and in an unprecised percentage of patients peripheral factors prevail on dyspnea as determinants of health status impairment.



Legend: In elderly COPD patients, the physical dimension, expressed by the walked distance as a fraction of the predicted and the Barthel Index, prevails upon the neuropsychological one, assessed by the MMSE, 15-GDS and EPESE questionnaire, in modeling the health status

Figure 3. Performance based dendrograms (source: SaRA) (from Antonelli Incalzi et al., 2009 [28], mod.).

In the SaRA study, it has been proved that 34% of people with mild to moderate bronchial obstruction (FEV1 = 50-79% predicted) were in the lower cluster of health status, whereas 15% of people with severe obstruction (FEV1 < 35%) were in the upper cluster [28]. Interestingly, clustering was primarily based on "physical" factors, and secondarily on affective/cognitive factors and sleep troubles (Tab. I). These findings explain the leading role of rehabilitation as a therapy for health status impairment in COPD: by improving physical capabilities, rehabilitation produces a notable improvement in health status, and age does not weaken, else it might strengthen this effect [29]. Furthermore, rehabilitation has the potential for smoothing the negative effect of peripheral factors, succeeding even if dyspnoea is not the main factor limiting the physical performance.

Exacerbations usually account for a temporary dramatic worsening of health status, as well as for a small residual permanent loss. Thus, each exacerbation marks a measurable drop in the involution of health status [30 31]. Accordingly, attempts at detecting and treating the exacerbations timely and, hopefully, at preventing them would translate in some slowing of health status decline.

Interestingly, patients with undiagnosed bronchial obstruction are characterized by a lesser impairment of health status, and this likely contributes to conceal the disease. Nevertheless, the impairment is clinically important [32]. Thus, unrecognized COPD is expected to contribute largely to the burden of disability in the elderly. This further stresses the need of performing any effort aimed at easing the diagnosis of COPD in the frail and multimorbid patient.

THE APPROACH TO COPD AS A FUNCTION OF PHYSICIAN'S SPECIALTY

Therapy of COPD encompasses a variety of pharmacological and non pharmacological options, being truly multidimensional in nature (see sections Papi and Pagano). However, these options are variably

Table I. Physician's approach to COPD problems as a function of specialty (from Paladini et al., 2011 [33], mod.).

	Geriatricians	Pulmonologists	Internists
Clinical awareness of the impact dynamic hyperinflation	54	86	61
Multidisciplinary approach	76,5	24	28
Use of indices of specific health status COPD	57	54	45
ADL/IADL evaluation	75	35	39
Phenotypic variability as an intrinsic feature of COPD	6	37	18

used depending upon the awareness of the patient's needs and the physician's cultural background. Thus, physician's specialty qualifies as a determinant of the approach to the elderly patient with COPD. Indeed, by comparing the attitudes of geriatricians, internists and pneumologists towards COPD patients Paladini et al found that the majority of geriatricians perform a comprehensive geriatric assessment and rate ADL/IADL performance and also frequently use disease specific health status instruments [33]. However, the awareness of phenotypic variability of COPD and of the important clinical role of dynamic hyperinflation is scarce among geriatricians. On the opposite, such awareness is higher in respiratory physicians, but, on the other hand, comprehensive assessment is out of their cultural patrimony and working habit, and even COPD-specific health status indexes are used slightly less commonly than by geriatricians. Finally, internists are characterized by a highly variable approach to the COPD patient, without any specialty-specificic trait, but with a basically monodimensional assessment (Fig. 4).

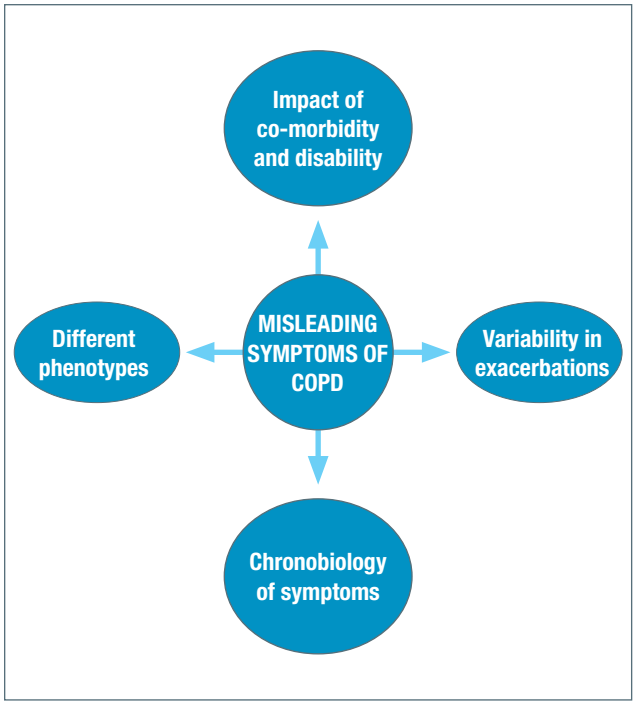


Figure 4. A tentative synthesis of determinants of variant symptoms in elderly COPD patients.

The assessment founds the awareness of individual problems and helps the physician to tailor the therapy. Thus, the specialty-specifics gaps suggest that a truly comprehensive and individually tailored therapy is the exception and not the rule for the elderly COPD patient. This is the basis for multispecialty education actions to improve the care of these complex patients.

CONCLUSIONS

COPD is a disease of age, but its clinical presentation also changes with age. As a consequence, physicians should be aware of the many diagnostic keys and pitfalls. They also should be able to translate the variegated clinical picture into a tailored multidimensional therapeutic strategy. Unfortunately, the dominant economic interest has promoted important pharmacological trials, but no trials testing comprehensive therapeutic strategies. Thus, reports about selected strategies of home care focus on a single domain, e g nurse based assistance or maintenance home rehabilitation, but they never tested an approach featuring the classical comprehensive geriatric assessment. Given that pharmacological trials could not improve survival, but only bronchial obstruction and health status, the time is ripe for such an effort being jointly sustained by geriatricians, internists and respiratory physicians.

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