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REVIEW

Impulse Oscillometry, Small Airways Disease, and Extra-Fine Formulations in Asthma and Chronic Obstructive Pulmonary Disease: Windows for New Opportunities

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Abstract: In recent years, the perspective of management of respiratory disease has been gradually changing in light of the increasing evidence of small airways as the major site of airflow obstruction contributing to the development of both COPD and asthma already in early stages of disease. First and foremost, the evidence is redefining disease severity, identifying small airways disease phenotypes and early signs of disease, and revising prevalence and overall epidemiological data as well. Much effort has been put toward the instrumental assessment of small airways' involvement and early detection. Several clinical trials have evaluated the advantage of extra-fine formulations which can best target the small airways in uncontrolled asthma and severe COPD. Here, we briefly present a practical overview of the role of the small airways in disease, the most appropriate diagnostic methods for quantifying their impairment, and provide some insight into the costs of respiratory management in Italy, especially in sub-optimally controlled disease.

Keywords: asthma, chronic obstructive pulmonary disease, small airways, impulse oscillometry, cost, extrafine particles

Introduction

As impulse oscillometry (IOS) is gaining more credit in the identification and classification of small airways impairment, the epidemiology of respiratory diseases is likely to change and will soon need careful recounting or, perhaps, even an updated classification.

Involvement of small airways is now known to be common in early phases of COPD and asthma, being correlated with disease stage severity. Recent IOS studies assessing small airways disease (SAD) among patients with asthma have estimated its prevalence as approximately 50–78% across all asthma severity stages,[1–3] whereas SAD affects up to 74% of COPD across all classes of GOLD classification (progressively increasing with increasing old and new GOLD stages) and is present in both COPD phenotypes, emphysema and chronic bronchitis.[4,5]

Such figures obviously translate into much larger target populations for pharmacological treatment: first, by englobing individuals with marked underlying SAD in the short term and, second, by curbing the population of severe COPD or asthma patients in the long term. To date, there are very few clinical and epidemiological studies addressing SA directly, and treatment guidelines have still to embrace the concept of SA within their recommendations.[6]

In view of these upcoming changes, our review aimed to present an overview of the involvement of small airways in respiratory disease and the diagnostic instrumentation available for its early detection. Also, it presents some economic data from Italy on treatment of COPD and asthma in the last decades, focusing on the advantages of early intervention.

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Literature Search

The present review was based on a thorough literature search (Pubmed, Scielo, and Scopus) based on the terms small airways (SA), SA anatomy, SA function, SA and asthma, SA and COPD, SA and respiratory function, disease burden and costs. Publications chosen for the review included narrative reviews, systematic reviews, meta-analyses, original articles, or public reports of national healthcare costs (in English or Italian), reflecting the most recent evidence available within the last decade. The search for publications on cost analyses initially considered publications addressing both national and international studies. However, given the lack of recent data referring to the Italian setting, the search was extended to consider a larger timeframe (last two decades) and focused on publications with contents specifically referring to the European and Italian setting.

Small Airways Disease: Definition

The term small airways (SA) is the anatomical term referring to the airways with an internal diameter <2 μm, starting approximately from the 8th generation [McNulty], thus embracing part of the conducting airways plus the acinar airways. With the exponential branching of airways at higher generations, the cross-sectional area reaches approximately 300 cm2 at acinar level, making the SA account for 98% of the total lungs. From an anatomical and physiological point of view, the SA feature typical anatomical characteristics such as a surfactant-lined surface and the lack of the mucous glands and cartilaginous support that distinguish it from the large airways. Airflow at this level is typically laminar and independent of gas density.[7,8]

Small Airways' Involvement in COPD and Asthma

In COPD, small airways become impaired by the indirect effect of smoke, pollutants or infections which concur in triggering airway remodeling, mucus plugging, and immune cell infiltration.[5] In particular, extensive damage can be found in the conducting terminal and respiratory transitional bronchioles, which significantly decrease in number by >40–56% already in early stages of disease (GOLD 1 and 2), whereas remaining SA are thickened with narrowed lumen.[9,10] In fact, several studies have shown SAD to be present before abnormal spirometry-assessed respiratory parameters are detected.[4,7,11] Importantly, SAD has a significantly relevant role in mild and moderate airflow reduction. CT and biopsy studies have confirmed the presence of SAD prior to ensuing emphysema, with neighboring anatomical areas featuring different levels of impairment (which may not yet be affected by emphysema).[9,10] In general, COPD patients with greater involvement of SA suffer increased hyperinflation, dyspnea, poor health status, COPD assessment test (CAT) > 10, and worse St. George's Respiratory Questionnaire (SGRQ) score.[7,9–11]

Differently, in asthma the SA often become sites of major inflammation appearing thickened with chronic inflammatory infiltrate consisting of eosinophils, T-lymphocytes, neutrophils, and macrophages. Density of lymphocytes and eosinophils in small airways is greater in the outer walls compared to the large airways. In addition, there is smooth muscle thickening and luminal occlusion by mucus.[7]

In its clinical manifestation, SAD correlates with worse symptoms, disease severity, greater functional impairment, exacerbations and more severe bronchial hyperresponsiveness compared to asthma with no SAD. In particular, the progression of disease in terms of aggravation and worse control, have been found to be associated with residual volume/total lung capacity (RV/TLC) and R5-R20,[1,2] R5, X5, AX and FRES,[1,12] worse forced mid-expiratory flow (FEF25–75%), forced vital capacity (FVC), RV and higher FENO, exercise or allergic-induced asthma symptoms and asthma-related night awakenings (Table 1).[1,2,12–15]

Because SAD contributes to reduction in airflow, increased airway resistance, gas trapping and non-uniform ventilation, SAD is thus detected by means of instrumental assessments that measure these variables.[7]

The current gold standard for diagnosing COPD or asthma is spirometry providing measures for FEV1, FEF25–75, FEV1/FVC, FEV3/FVC, FEV/SVC, yet it is not a reliable marker for early disease or specific for SA. FEV1 mostly expresses large airway obstruction, whereas FEF between 25–75% (ratio of forced vital capacity to relaxed vital capacity) expresses mid-portion airway.[7] Likewise, in COPD, FEV1 and FVC have been shown to be unsensitive to damage to the small airways especially in the early phases of COPD.[5,16] However, FEV3/FEV5 may in fact represent an

Table 1 Characteristics of SA Phenotype in Asthma and COPD

	Asthma	**COPD**
Demographic		
	Older age, longer smoking history, longer onset of disease, overweight.[1,11]	Smokers /ex heavy smokers.[9]
Respiratory function		
	Greater functional impairment (lower FEF, FEV1/FVC, RV, higher FENO), more severe bronchial hyperresponsiveness, exercise or allergic-induced asthma symptoms, asthma-related night awakenings.[1,11,13]	Poor spirometry results/ expiratory flow limitation, gas trapping; increased pulmonary hyperinflation (leading to dyspnea and functional limitation, and potentially to development of comorbidities); dyspnea (MRCS).[9]
Inflammatory markers		
	More eosinophils in late phase sputum.[11]	Increased macrophages, neutrophils, CD20+ B cells, CD4+ and CD8+ T cells (CD8+ predominant).[5]
Clinical manifestations		
	More severe symptoms, more exacerbations.[1,11]	Poor health status/ greater impact.
Others		
	Non atopic late onset asthma; lower pH in alveolar breath condensate associated with local and systemic eosinophil inflammation.[1,11]	Worse QoL (SGRQ), CAT.[4]

Abbreviations: CAT, COPD Assessment Test; MRCS, Medical Research Council Scale; SGQR, St George's Respiratory Questionnaire.

earlier and more sensitive spirometry marker of SA assessment,[3] even if R5-R20 was more sensitive than FEV3/FEV6 to intercept SAD in asymptomatic smokers with normal spirometry.[11] In fact, as recently evidenced by a cohort-based study of over 24,000 individuals of general population (Moli-sani study), abnormal values of FEF25–75 (defined as < lower limit normal values) are associated with a 33% increased risk in total mortality.[17]

When feasible, the presence of an abnormal FEF25–75 should be supported by other pulmonary function assessments to i) determine the abnormal resistance of the peripheral airways district (detected by IOS) and ii) evidence air trapping (measured by closing volume or residual volume, plethysmography), which together with altered FEF25–75 define involvement of the small airways.[17]

Many studies assessing the diagnostic sensitivity for SAD seem to agree on the greater accuracy of measurements by IOS, which applies pressure to airways at a range of frequencies and can measure components of respiratory impedance, including resistance and reactance. Resistance is the in-phase component of lung impedance and provides information about the forward pressure of the conducting airways, whereas the reactance is the out-of-phase component of lung impedance and expresses the capacitive and inertive properties of the airways. Resistance at 5 Hz (R5) and 20 Hz (R20), respectively, represent total airway resistance and proximal airway resistance, while the difference between R5 and R20 measures peripheral airway resistance. The reactance at 5 Hz (X5) reflects the combined effect of tissue elastance and inertance.[13,18]

A recent international study on a cohort of over 700 asthma patients with varying disease severity aimed to identify which combination of biomarkers, physiologic tests (spirometry, body plethysmography, MBNW, IOS) and imaging tools best expressed SAD and its association with disease severity.[2] Results showed the best instrumental combination for assessing SAD prevalence is IOS plus spirometry (which contributed most to SAD score and differentiated between SAD groups). While IOS-measured R5-R20 was found to be the marker most closely correlated with SAD.[2] Recent results from the one-year longitudinal arm of the study confirmed that SAD predicts asthma control and exacerbations; in detail: R5-R20, AX, X5 and FEV1 were significantly correlated with asthma control, while FEV1 and R5-R20 were significantly correlated with QoL.[12]

Another recent study evaluating the diagnostic value of IOS in the detection of small airway dysfunction in subjects with COPD/asthma-like symptoms and preserved pulmonary function, confirmed the higher sensitivity of IOS in detecting SAD compared to spirometry and its higher correlation of R5, R20, Fres and AX with symptoms.[19]

In any case, other traditional tests may be used, either alone or in association.

Whole body plethysmography (measuring RV1, RV/TLC, airways resistance) is sensitive to lung hyperinflation and gas trapping, providing several markers for SA involvement. RV correlates with level of inflammatory changes in COPD and peripheral airway resistance in asthma. In COPD where TLC is generally higher, RV/TLC is a more reliable marker of gas trapping and small airway impairment.[5]

Inert gas washout (single and multiple nitrogen washout) measures the mixing of gas, depending on the structure of the larger and smaller airways. Airway diseases affect the lung differently, causing differences in ventilation. In obstructive lung disease the closing volume is increased due to the premature airway closure which occurs as loss of elastic recoil caused by emphysema or SAD. Multiple breath washout can detect SA involvement already from 10-pack years vs 20-pack years assessed by spirometry. Analysis of the Phase III slope can provide information on ventilation in different parts of the lungs.[5]

Assessment of SA can also be performed by exhaled nitric oxide (measured as FE_{NO}), which is traditionally used in asthma. High NO concentrations are found in alveoli in mild and severe asthma and COPD (though raised FE_{NO} in COPD is lower than in asthma).[7] Measurement of exhaled NO can provide information on the presence and location of inflammation (especially eosinophilic inflammation) in the central or peripheral airways of the lung.[7]

Finally, CT imaging is useful for discriminating different phenotypes and localizing heterogeneity.[7]

Figure 1 proposes a summary of non-invasive assessments for SA involvement, as proposed by Santus et al in their exhaustive review on the relevance of targeted treatment in SAD.[20]

Treatment of Small Airways with Extra-Fine Bronchodilators and Inhaled Corticosteroids

Taken together, the evidence on the involvement of SAD in COPD and asthma and the potential for targeting the SA have encouraged a number of clinical studies to review the efficacy of extra-fine inhaled formulations (< 2μm) in SAD-related outcomes, in particular those assessed by IOS. Newer inhaled extra-fine formulations for COPD and asthma include inhaled corticosteroids (ICS), ICS plus a long-acting beta agonist (ICS-LABA), and combinations of ICS/LABA plus a long-acting muscarinic antagonist (LAMA) ICS/LABA/LAMA.

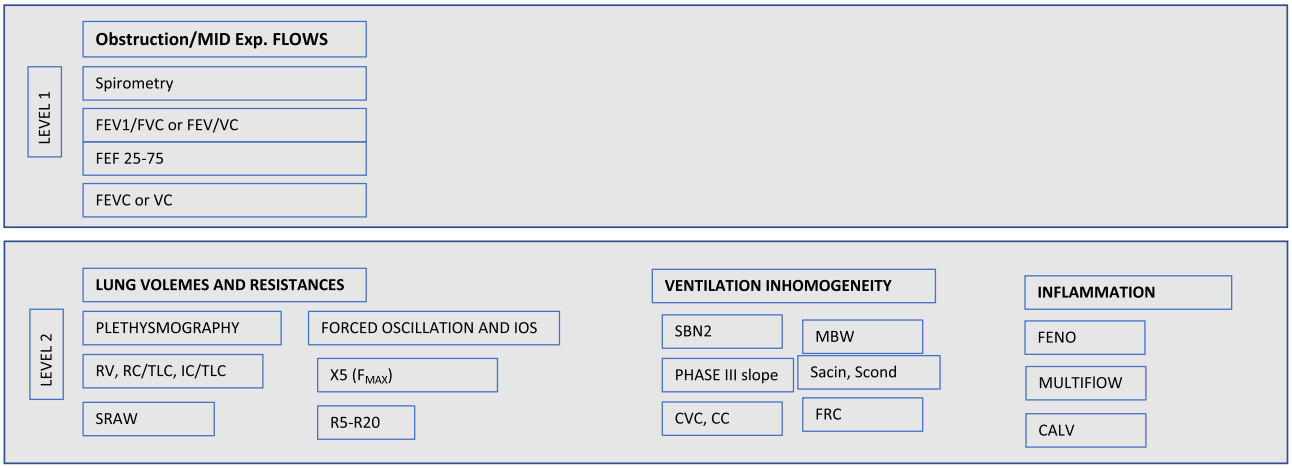

Figure 1 Assessment strategy for small airways.

Notes: Adapted and used with permission of Daedalus Enterprises Inc, from Santus P, Radovanovic D, Pecchiari M et al. The Relevance of Targeting Treatment to Small Airways in Asthma and COPD. *Respiratory Care*. 2020, 65 (9) 1392–1412; permission conveyed through Copyright Clearance Center, Inc.[20]

Compared to traditional formulation with fine (2.1–5 µm) or coarse-size (5 µm) particles, the reduced particle size of extra-fine beclometasone dipropionate (BDP)/formoterol fumarate (FF), and BDP/FF plus glycopyrronium bromide (GB) in newer formulations have allowed a more uniform drug delivery to the lungs in both large and small airways, regardless of the presence of a respiratory condition (asthma or COPD).[8,21] The deposition pattern in the lungs was also recently investigated by Usmani et al by means of functional respiratory imaging to simulate aerosol distribution.[22] Findings confirmed that administration of extra-fine BDP and FF and BDP, FF and GB delivered by pMDI to patients with moderate/severe COPD (FluidDA database) yielded a mean central:peripheral (C:P) ratio indicating a higher deposition in the small airways than in the large airways.[8,21–23]

The PRospectIve Study on asthMA control (PRISMA) study evaluated over 2800 asthmatic patients from 52 Italian centers.[24,25] The cross-sectional phase confirmed better control (evaluated by asthma control test, ACT) and QoL (EQ-5D) with ICS/LABA compared to other treatments –leukotriene receptor antagonist (LTRA), beta$_2$-agonists, ICS, system ICS, ICS plus short-acting beta-agonists (SABA).[24] In particular, among the ICS/LABA combinations used – BDP/FF, budesonide/formoterol (BUD/F) and fluticasone/salmeterol (FP/S) – patients treated with extra-fine BDP/FF were 40% more likely to attain control and perceive a better QoL compared to large-particle BUD/F and FP/S.[24] These findings on the greater effectiveness of extra-fine particles are in line with another study which compared initiation of treatment with an extra-fine (ciclesonide) vs fine-particle (FP, or non-extrafine BDP) IC. Results confirmed better 1-year asthma outcomes and fewer changes to therapy with the extra-fine IC.[26]

The difference between large vs extra-fine ICS was also evaluated in COPD patients either beginning or stepping-up their dose of extra-fine BDP or FP.[27] The study was a retrospective matched cohort analysis and assessed treatment change and COPD exacerbations, defined as emergency care/hospitalization for COPD, acute oral corticosteroids, or antibiotics for lower respiratory tract infection, over a 2 year follow up. In the initiation sample there were comparable effects on exacerbation rates obtained using significantly lower doses of small-particle ICS vs higher doses of larger-particle ICS, however initiation with small-particle ICS was associated with better odds of treatment stability throughout.[27] Increase in dose was required in > 50% of BDP group, while an additional treatment was required in the FP group; the BDP group was also exposed to lower mean ICS. Similar trends were observed for the step-up sample; the adjusted odds of treatment stability and treatment change were similar in the two cohorts.[27]

The extra-fine particle size appears to also have a role in reducing occurrence of pneumonia and non-pneumonia related respiratory tract infections. Several recent randomized controlled trials have found higher risk of pneumonia linked to the regular use of any inhaled corticosteroid (ICS) compared to use of non-ICS treatments especially in COPD.[28] In particular, the risk of pneumonia changes with ICS subclass and is lower when using extra-fine ICS at lower ICS doses.[29–31] Nonetheless the topic is still subject to debate; a network meta-analysis comparing nine combinations of ICS/LABA/LAMA in COPD found significantly lower pneumonia infections only with the fluticasone propionate (FP)/glycopyrrolate/salmeterol (SAL).[31]

Further evidence on the relationship between distribution to small airways and better clinical control is provided by a recent study specifically assessing the efficacy of an extra-fine formulation of beclomethasone dipropionate/formoterol fumarate (BDP/FF) 100/6 µg b.i.d in COPD patients with SAD.[32] The study measured fall in resistance from 5 to 20 Hz (R5–R20) and residual volume/total lung capacity (RV/TLC) ratio by impulse oscillometry, spirometry, and plethysmography. Treatment resulted in R5–R20 significant change from baseline [0.23 ± 0.09 kPa/(l/s)] to V2 [0.16 ± 0.09 kPa/(l/s)] and V3 [0.16 ± 0.08 kPa/(l/s)] ($p< 0.05$). Clinical status was also significantly improved compared to baseline: the CAT score changed from an average baseline value of 13–6 and 4 (V2 and V3, respectively) ($p<0.05$). A correlation was found between CAT percentage change values and the corresponding ones of R5–R20 and RV/TLC.

Treatment outcomes in COPD with SAD were also assessed in a recent review by Usmani et al.[5] The study provides a detailed comparison of extra-fine ICS/LABA, co-suspension LAMA/LABA, and ICS, novel inhaling systems, and other newer agents in development, confirming the advantage of extra-fine particle sizes in reaching peripheral areas and in improving function and reducing exacerbations in SAD phenotypes.[5]

As for asthma, a pilot study by Carpagnano et al compared treatment efficacy of clinical control and inflammatory profile in small airway (SA) vs non-small airway (NSA) phenotypes. The study included a group of patients with

moderate uncontrolled asthma on treatment with medium dose ICS/LABA fixed combination + SABA as needed, who had indication of step-up to high-strength extra-fine pMDI BDP/FF (200/6 μg) in fixed dose at a daily dose of 800/24 μg as step-up therapy. Overall, patients with the small airway phenotype (SAP) featured, at baseline, worse functional (FEF 25–75%, FVC, RV) and inflammatory impairment.[13] High strength extra-fine pMDI BDP/FF treatment (both active ingredients as extra-fine formulation) improved disease control in both groups (in terms of asthma control test ACT, and asthma control questionnaire ACQ), but greatest improvements were found for patients with the SA phenotype, thus encouraging future phenotype-based treatment strategy. Importantly, the study also assessed efficacy of the extra-fine formulation in terms of biological markers of SA inflammation, finding a reduction of FENO350 and late phase sputum eosinophils, and an increase of alveolar breath condensate.[13]

Costs of Treatments and Diagnostic Assessments

Over the years, there have been numerous reports on Health Care (HC) costs for asthma and COPD, confirming the high burden borne by HC systems, with costs for patients with respiratory disease in advanced countries being approximately at the fifth position of overall HC costs.[33–37]

Extensive data on the economic burden of respiratory diseases in Europe are provided by in an-depth cost-of-illness analysis based on a systematic literature search to identify published research, and on data from national registries, WHO, and Eurostat databases.[33] The findings confirm COPD and asthma as representing the greatest economic burden among respiratory diseases. In detail, the annual cost of healthcare and lost productivity for COPD and asthma across the 28 EU member countries was estimated to be €48 billion and €34 billion respectively – with a magnitude of indirect vs direct costs similar for both COPD and asthma, and slightly higher indirect costs for COPD.[33]

The Relevance of Costs in Daily Clinical Practice

Shifting to a bottom-up perspective, several studies have highlighted significantly larger HC expenditures for patients with uncontrolled vs controlled respiratory disease (worse disease severity) and documented how early interventions (newer diagnostic tools and targeted treatments) translate into overall cost reductions for hospital and emergency care.[39–47]

In the following paragraphs, we provide an economic focus of HC expenditures in Italy over the last two decades, reviewing the few reference studies available at national level. Unfortunately, these do not include any data on costs related to SAD, since there are still no specific studies on SAD treatments or cost burden. As the awareness of SA involvement become more widespread, we expect to see new clinical studies designed around SAD-relatedendpoints in the near future.

A Focus on Italy: Data from the Last Two Decades

Cost Analysis for Asthma

Estimates on the cost of illness for asthma in Italy are based on two reference studies by Accordini et al – currently, the only studies available.[45,46] The first is an Italian cost of illness study for asthma assessing data from 2000 on over 500 patients which estimated the average yearly cost per patient as €741, of which 43% represented direct costs (47% for medication, 23% hospitalizations) and 57% indirect costs.[45] In particular, costs for well-controlled asthma were approximately 3.5 times lower than poorly controlled asthma (which alone accounted for 46% of total expenditures). The difference in cost between controlled and uncontrolled asthma was further confirmed in another study by Accordini et al at European level (Belgium, Estonia, France, Germany, Iceland, Italy, Norway, Spain, Sweden, Switzerland and the UK).[46] The cost estimates were computed from the societal perspective following the bottom-up approach on the basis of rates, wages and prices (obtained at the national level from official sources) and were then converted to the values at the time of the study. The authors quantified the costs of persistent asthma of over 460 European adults (30–54 yrs) as €509 in controlled asthma vs €2,281 (of which > 60% indirect costs) in uncontrolled disease, suggesting proper asthma control as a cost-saving strategy (Table 2).[46] As in the previous study, the lack of disease control was the strongest determinant of the individual total cost, being 3-fold higher among uncontrolled subjects.[46]

Other useful estimates are provided by the Social Impact of Respiratory Integrated outcomes (SIRIO) based on data from the Italian NHS of real-life health resource consumption,[40] and a 2016 update.[41] Economic assessment evidenced

Table 2 Mean Total Costs for Asthma and COPD per Patient in Italy

	Mean Total Annual Costs per Patient (€)	Mean Total Cost (€)	Mean total cost (€)	Notes
Study (First Author/Year)		**Controlled**	**Uncontrolled**	
Asthma				GINA classification
Dal Negro 2002.[38]	Not specified	608	2,457	
Accordini, 2006.[45]	741	379	1,341	Italian setting
Accordini, 2013[46]	1,583	509	2,281	Extended to EU setting. Over 60% are IC.
Dal Negro, 2007[40]	1,177.40	7,345	2,862	Figures for controlled -uncontrolled are derived from intermittent - severe
Dal Negro, 2016[41]	1,290.89	709,30	2,636.76	12 months FU. Figures for controlled - uncontrolled are derived from FEV1% ranges.
COPD				GOLD classification
Dal Negro, 2002[38]	1,801	1,500	3,912	
Dal Negro, 2008[42]	2,723.7	1,1314.96	5,451.7	
Dal Negro, 2015[43]	3,291	Not specified	Not specified	+ 20.8% compared to 2008 costs. 89.1% are DC, of which 59.9% for hospital care.

Notes: Data are those reported in recent cost studies with a bottom-up approach. Costs are expressed as mean for a 12-month observation period.
Abbreviations: DC, direct costs; IC, indirect costs; FU, follow up.

that compared to 2007, total annual cost/patient has decreased significantly.[40] This shift was attributed by the authors to the widespread adoption of GINA guidelines, progressively increased awareness of asthma burden, and increased therapeutic appropriateness in recent years. In particular, the study reported a decrease in hospitalization costs, with an increase of pharmaceutical costs for medication which accounted for 66% of the total asthma cost.[40,41] Hence, these data confirm that better disease control is an effective cost-saving strategy.

Cost Analysis for COPD

Similar findings were found for COPD (Table 3) in the Italian studies building on data from 2002, including the SIRIO study.[39,42–44] In 2008, annual costs per patient calculated at baseline index visit were €2,506.8 and after a 12-month follow up €2,044.6, evidencing a €462.3 decrease. In detail the pharmaceutical costs increased to €361.5, but the expense led to a twofold saving on hospital and emergency care – which decreased by €718.6 – and on indirect cost by €128.5. Cost estimates for total mean annual costs are listed in Table 2.[42–46] Decreased expenditure after treatment was also reported in the 2015 UPDATE study with costs decreasing at follow up by 17.7%.[43]

As to the breakdown of cost items making up the overall annual costs in COPD, data from the Continuing to Confront COPD International Patient Survey for Italy yielded results of 27% of costs for hospitalization, 40% home oxygen, 15% medications, 5% specialist visits, 7% GP visit, 3% moderate exacerbation, and 3% severe exacerbation.[47]

When looking at resource utilization from a perspective of level of disease control, it is interesting to notice the dramatic difference in costs for patients with severe COPD exacerbations (compared to patients at all levels of disease). Indeed, according to a study based on the administrative records of over 15,000 Italian COPD patients, the overall annual cost in the case of patients hospitalized for "severe" COPD exacerbations would add up to €6,725 per person (95% CI 6,590–6,863).[48] A recent 2018 systematic review comparing COPD cost data from several EU countries highlighted the relevant role of prescriptions as the main cost-driver in the maintenance phase – due to the addition of antibiotics and oxygen therapy requirement – and was directly proportional to the frequency of exacerbations and severity of disease. With specific mention to Italy, the mean prescription cost added up to €1,404.[49]

Table 3 Prevalence of Drug Use in Treatment for Asthma and COPD by Treatment Class in Italy

Drug Type	Prevalence of Use (%)	
	Asthma	**COPD**
Monoclonal antibodies	0.1	0.1
Antileucotriens	3.5	1.7
Theophylline bronchodilator	0.7	2.7
Cromomes	NA	NA
ICS	8.6	11.1
PDE-4 inhibitors	NA	NA
LABA	0.7	1.7
LABA + ICS	15.9	17.6
LABA + LAMA	0.3	4.4
LAMA	3.0	22.3
LAMA + LABA + ICS	0.3	3
SABA	7.7	5.5
SABA + ICS	0.8	0.7
SABA + SAMA	1.8	3.9
SAMA	0.5	1.7
ULTRA-LABA	0.1	1.8
ULTRA-LABA + ICS	4.8	9.1

Notes: Modified from Rapporto OSMED 2020.[51] Numbers of patients in treatment for specific category over the total number of patients diagnosed with asthma or COPD.

Costs: COPD vs Asthma

The overall direct expenses for the public HC system for patients affected by COPD are up to four-fold those for patients with asthma.[50] An Italian cost analysis on use of ICS/LABA in asthma and COPD, estimated that costs related to respiratory disease per patient/year were €2,268.97 in COPD vs €535.77 in asthma: of this expense, 67% accounts for respiratory medication (approximately €488.28/year/patient) and 27.63% for hospital care (rate was 22.0% in COPD vs 2.9% in asthma).[50] As pointed out by the authors, findings on the higher drug use may also reflect the sub-optimal treatment of the disease and costs ensuing from complications due to non-adherence to treatment. Indeed, adherence remains quite a relevant aspect in overall management and proper resource allocation, as rates in COPD and asthma are quite low (generally <50%), and variable depending on severity of symptoms (47% adherence, defined as 80% drug coverage over one-year assessment period among BPCO, and 15% for overall drugs prescribed for obstructive respiratory conditions).[50,51]

Therapy-Related Costs

Based on the 2020 report by the Observatory of the Italian Medicines Agency (OSMED) documenting a seven-year observation period, respiratory disease therapies in 2020 represented the seventh highest public expenditure item among therapeutic classes (5.7% of public spending), accounting for €1,305.6 million.[51] Table 3 lists the prevalence of drug use in treatment in asthma and COPD by treatment class in Italy (Table 3).

In general, several studies have evidenced savings on treatments with earlier interventions and when keeping the disease well controlled, as seen in Tables 1–3 .[36–46]

So far, however, comparisons on specific voice items remain difficult due to the lack of equivalent indicators for some geographical areas. In the case of Italy, specific data on pharmacological costs are sparce, though a rough estimate can be gained from other countries with similar healthcare systems in the EU. One Spanish study calculated COPD-related healthcare costs and exacerbation rates in patients on multiple inhaler triple therapy within 30 days (early treatment group) of index visit or after 30 days (31–180 days, late treatment group) from exacerbation.[52] The results confirmed a lower healthcare resource consumption in the early-treated group. In detail the savings in therapy was €98 (from 1,122 vs 1,024). The patients with more than one exacerbation in the 12-month follow up period were 28% when treated early, compared to 36%, with an exacerbation rate of 0.5 vs 0.6 in one year (p=0.022).[52]

One analysis specifically focused on initiating therapy with an extra-fine or standard-size particle IC in asthmatic patients which provided cost-effectiveness data for the UK healthcare system.[53] As the many studies reported, use of extra-fine formulations led to a higher efficacy and lower overall costs. The odds of overall control (defined as: no hospitalization or oral steroids for asthma, no antibiotics for lower respiratory infection, limited reliever use) increased from 70% and was greater for extra-fine ICS (OR: 1.23, 95% CI). Total reduction in asthma-related costs (when adjusted for baseline confounders) during the follow up was – £66 (from £93 to 37). Extra-fine-particle ICS was the preferred treatment (less costly and most effective) in 92% of cases. It is noteworthy to mention that the study is the first cost-effectiveness assessment using the same metrics, despite the large differences in the two healthcare systems evaluated.

Finally, a systematic review by Menzella et al,[54] exploring the pharmacoeconomic aspects in asthma treatment, highlighted the optimization of pharmaceutical expenses thanks to controller medications and innovative therapies and the increase in prescriptive appropriateness (which translated into evident saving on hospitalizations). The authors also conclude stressing the need for accurate phenotyping and identification of predictors of response.[54]

Diagnostic Assessments

It is noteworthy to underline that, while direct costs are driven mainly by hospitalization, the costs for the diagnostic and the investigational approach to the disease still represent a minor proportion of the total burden of illness cost (5–6% only).[41,45]

Once considering, for example, the adoption of investigation methods for airway resistance on a larger scale than the current practice, the incremental cost for each procedure (23,24€ - RESISTENZA DELLE VIE AEREE - codice 89.38.1 Tariffario Nazionale Procedure Ambulatoriali) will be very low and negligible when compared to the total burden of care for asthma and COPD.[55] Especially in more compromised and more costly patients (severe or uncontrolled), this investigational procedure will provide the opportunity to implement the most appropriate therapy with extra-fine formulations providing, at a very marginal additional cost, an expected beneficial effect also in economic terms. Although not conclusive, the study performed in UK and USA has highlighted how the use of extra-fine-inhaled corticosteroid could represent a cost-effective approach, with extra-fine (beclametasone) versus standard size-particle (fluticasone in this publication) inhaled corticosteroid not only more effective but also less costly (−17/30%).[53]

Table 4 provides unit cost per item as available from the studies mentioned previously.

Social Aspects and Compelling Need for New Strategies

The aspect of care in respiratory diseases cannot be discussed outside the broader scope of social changes in terms of aging population, shifting demographics, and changes in family and community networks.[56]

Asthma is more prevalent among the younger population of productive age and has an economic cost due to loss of productivity. Conversely, COPD is more prevalent in the aging population and features ever increasing costs to front complications from chronic and comorbid conditions.[57]

With the aging of the population, it is estimated that in 2050, there will be a much greater population of elderly (> 65 yrs), with two elderly individuals for every one individual of productive age. Specifically, the percentage of independence (the ratio between the population > 65 yrs and the population between 15–64 yrs) is predicted to go from 30% in 2010 to 60% in 2050; while the aging index (accounts for all effects associated with life expectancy and evolution of childbearing) will go from 150- to 300. Moreover, based on the care index (ratio between individuals in need of health assistance over those in central age range 30–59 by 2050) there will be 3 individuals in need of care for every four adults.[56]

Table 4 Unit Costs per Main Items of Direct Costs

	ASTHMA				COPD		
Source (First Author, Yr Publication)	**Accordini 2006[45]**	**Accordini 2013[46]**	**Dal Negro 2007[40]**	**Dal Negro 2016[41]**	**Sicras Mainar 2019[52]**	**Dal Negro 2008[42]**	**Dal Negro 2015[43]**
	Unit Cost (€)	Unit Cost (€)	Range Mean Annual Cost/ Patient (BL - FU) (€)	Unit Cost and Range Mean Annual Cost/Patient (BL - FU) (€)	Unit Cost (€)	Unit Cost and Range Mean Annual Cost/Patient (BL - FU) (€)	Range Mean Annual Cost/ Patient (BL - FU) (€)
Medical consultations (overall)	–	34	112–56	–	–	150–93	–
GP	13	–	–	15.7 13–5	23.19	–	–
Specialist	20	–	–	20.66 18–23	67.50	–	–
Tests (overall)	–	–	128–56	–	–	163–125	
Spirometry	33	–	–	–	15	–	–
Skin prick	23	–	–	–	–	–	–
Blood, hemochrome, and sepcific IgE	108	–	–	–	22.3	–	–
Bronchodilator tests	–	–	–	–	56	–	–
CT	–	–	–	–	92	–	–
MRI	–	–	–	–	154	–	–
Pharmaceutical (overall)	–	–	–	–	–	–	–
Main resp. medication	Market price	–	399–717	Market price 636–851	Market price	347–663	498 −547
Hospital care (total)	–	–	–	2.537 218–104	–	1,519–823	1,970–1,569
ED visits	100	100	5.11–2.75	–	117.53	7.6–3.8	–
Admission to IC	–	823	348–122	–	–	–	–
Chest medicine	–	390	–	–			–
Other wards	–	370	–	–	320.90/ day	–	–
Day hospital, outpatient	–		113–24	–		89–70	463–344

Notes: Costs reported for asthma: data on unit costs are those from the multicenter retrospective study by Accordini et al 2013 on a broad representative EU sample.[46] The mean annual costs for asthma are derived from Dal Negro 2007[40] and represent the mean cost at index visit and after 12 months after starting specialist care, in detail the cost for hospitalization was calculated as the mean cost for asthma relapse according to the National Diagnosis-Related Group (DRG) tariffs; pharmaceutical cost was obtained by adding the cost of all respiratory drugs directly related to asthma treatment. The greatest cost decrease in annual costs was reported in patients with the severe form (data not shown).[40] Costs reported for asthma: costs for COPD are from the multicenter perspective studies by Dal Negro et al 2008 and 2015 and are given both as unit cost (where available) and as the mean cost at index visit and after 12 months after starting specialist care.[42,43] In detail: the hospital cost was evaluated as the mean cost of intensive care unit and hospital admissions for COPD exacerbation and chronic/acute respiratory failure - ie, the principal treatment, by daily dose and duration of administration; the costs for examinations and for specialist's visits were derived from national inpatient tariffs. Unit costs for COPD are also provided by the Spanish study by Mainar et al 2019.[52]

In addition to having evident implications as to direct healthcare costs, such changes will inevitably present dramatic social implications for sustainability over time. To date the burden of informal care (beyond what is provided by public healthcare) is mostly absorbed by families. In the coming decades, with families becoming more spread out in terms of geographical location and of fewer components, the support from productive/active family members appears to be dwindling. Accordingly, there is a compelling call for a restructuring of the care model, as well as of strategies that can delay disease progression and increase the QoL of patients with chronic debilitating conditions.[56,58]

IOS in Clinical Practice

Despite some studies on prediction models for costs in respiratory diseases, predictions on future trends can be offset by unforeseen changes over time, such as breakthroughs in technology or drugs available, changes in HC protocols and guidelines, or unpredicted pandemics such as the recent SARS-cov-2.[39] Accordingly, we expect economic predictions to be updated in light of the new role of SA in asthma and COPD, the better performance by IOS in SAD detection, and extra-fine treatments. A study by Herse had calculated roughly a 50% increase in costs for COPD from 2010 to 2020, but such figures are most likely no longer generalizable to the current setting.[58]

Currently, IOS is already in use in many specialist centers for follow up in patients diagnosed with SAD. In consideration of the advantages in terms of early detection, IOS should become a first-line diagnostic tool for early diagnosis in individuals at risk (eg, smokers), or mild COPD, alongside spirometry; not in patients with respiratory failure (ie, receiving oxygen ventilation therapy). Ideally, it should also have a role in smoking cessation clinics as a motivational tool, showing the patient the underlying lung damage despite normal spirometry values (FEF 25–75% cannot be considered a reliable parameter).[12] So far, limits to the inclusion of the test in standard COPD management protocols are represented by the few resources for purchase and/or functioning of instrument; time of examination in relation to visit with pneumologist.

As for asthma, IOS would certainly be relevant as a second-line tool in more severe or treatment-resistant phenotypes, uncontrolled asthma, and follow up of patients with severe asthma treated with disease-modifying drugs. Ideally, because of the additional information, IOS could be extended to all asthma patients at an early phase.[6]

Importantly, where IOS is not feasible due to lack of resources, the evaluation of SAD should be performed in case of poor respiratory control or exacerbations which could lead to the suspicion of SA involvement.

Lastly, in consideration of the ongoing pandemic, IOS use could be considered in the follow-up of COVID patients, and in patients with long-COVID featuring persistence of mild symptoms over time, despite having had a mild form of the disease (spirometry is in range, slightly impaired diffusion).

Future Research

Today, the knowledge on SAD appears to offer a new window of opportunity for treatment in COPD and asthma. However, the concept of SAD has still to be embraced in the setting of clinical trials so to provide updated clinical data relevant to clinical practice.[1] Meanwhile, while awaiting new recommendations being issued and management algorithms being developed, some steps forward can be made in clinical practice and structuring of pathways of care. Table 5 presents a brief needs analysis based on the critical areas in respiratory care and proposed paths to improvement, in light of latest advances, ie, early screening, diagnostic instrumentation and treatment available for COPD and asthma.

Conclusion

The present review aimed to describe the current evidence in literature on the small airways, the measurement of its involvement, and the potential of early intervention in management of chronic disease. Despite the lack of data from clinical studies directly addressing SA, current evidence supports assessing possible SA involvement in early stages of COPD and asthma, so to prevent development/worsening of exacerbations, and complications from long-term chronic disease. The present review also presents a summary of the sparse data available for COPD and asthma health-related costs in Italy. Despite the lack of updated figures, data converge to show higher management costs for poorly controlled disease, pointing to the potential benefits derived from early intervention and consideration of SAD.

Table 5 Needs Analysis. Interventions/Next Steps That Need to Be Undertaken in Order to Upgrade Current Practice to the Next Level

Steps Toward Improvement	Promoters
A) Review/update perspective on respiratory disease	
- epidemiology of asthma and COPD based on newer consolidated technologies	Clinical researchers, scientific community
- treatment thresholds	Clinical and pharmaceutical researchers, scientific community
- treatment targets	Clinical and pharmaceutical researchers, scientific community
- quantify savings from shift from uncontrolled to controlled disease	Clinical researchers, scientific community, pharma, health economist
B) Define new models of care, other than hospital/specialist	
- implement local networks coordinating hospital, specialistic hubs and general practitioners	National, regional and local HC policy-makers, representatives for specialists, GP, patient associations
- circulate usable information on network among all stakeholders (contacts, addresses, operational hours, and roles of specialists, general practitioners, healthcare providers, patients, social services, and schools)	Regional and local HC policy-makers, representatives for specialists, GP, patient associations
- provide patients contact information on professional figures involved other than pneumologist and when these professionals should be consulted (respiratory therapist, specialist nurse; nutritionist)	Regional and local HC policy-makers, representatives for specialists, GP, patient associations.
- create automatic monitoring systems to alert HCP of extended healthcare "inactivity"	National, regional and local HC policy-makers
C) Optimize availability of diagnostic tools	
- upgrade diagnostic armamentarium based on breakthrough evidence	National, regional and local HC policy-makers, hospital managers
- implement use of IOS in patient populations	National, regional and local HC policy-makers, scientific societies, hospital managers
- include more advanced assessment in initial screening visit	National, regional and local HC policy-makers, scientific societies, hospital managers
- streamline diagnostic investigations to reduce times in waiting lists	National, regional and local HC policy-makers, hospital managers
D) Implement targeted pharmacological treatments	
- extra-fine particle dispenser	Specialists, pharmacists, and GPs
- reduce inappropriate prescriptions	Specialists, pharmacists, and GPs
- intervene in underlying issues of non-compliance	Specialists, pharmacists, and GPs
E) Redefine treatment plans for COPD and asthma	
- implement early screening in at-risk subjects	National, regional and local HC policy-makers, scientific societies, specialists, GPs
- holistic/integrated management strategy in consideration of comorbidities, level of independence and functional status	National, regional and local HC policy-makers, scientific societies, specialists
- actively plan with patient personalized strategy to prevent relapse, acute events, disease progression, and functional decline.	Specialists, respiratory therapists, GP, family member/informal caregiver, HC policy-makers
- address dyspnea and muscle fatigue in overall patient management	National, regional and local HC policy-makers, scientific societies, specialists, respiratory therapists

Note: Steps (and promoters for each step) are split into five main areas of intervention (A-E).
Abbreviations: GP, general practitioner; HC, healthcare.

Abbreviations

ACQ, asthma control questionnaire; ACT, asthma control test; BDP, beclometasone dipropionate; C:P, central:peripheral; CAT, the COPD assessment test; COPD, chronic obstructive pulmonary disease; EQ-5D, European Quality of Life Five Dimension, and EuroQol five-dimensional; FEF, forced expiratory flow; FEN0, exhaled nitric oxide; FF, formoterol fumarate; FP, fluticasone propionate; FVC, forced vital capacity; GB, glycopyrronium bromide; GOLD, Global Initiative for Chronic Obstructive Lung Disease; ICS, inhaled corticosteroids; IOS, impulse oscillometry; LABA, long-acting beta agonist; LAMA, long-acting muscarinic antagonist; LTRA, leukotriene receptor antagonist; NSA, non-small airway; OSMED, Observatory of the Italian Medicines Agency; PRISMA, PRospectIve Study on asthMA control; R, resistance; RV, residual volume; SABA, short-acting beta-agonists; SAD, small airways disease; SAP, small airway phenotype; SIRIO, Social Impact of Respiratory Integrated outcomes; SGRQ, St. George's Respiratory Questionnaire; TLC, total lung capacity; yrs, years.

Ethics Statement

The present review did not involve original research activity on patients nor the use of data containing confidential information, therefore does not require approval from Institutional Review Boards.

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All authors contributed to data analysis, drafting or revising the article, have agreed on the journal to which the article will be submitted, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

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