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Impact of an integrated disease management program in reducing exacerbations in patients with severe asthma and COPD

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Summary
Background: Conflicting data exists on the effectiveness of integrated programs in reducing recurrent exacerbations and hospitalizations in patients with Asthma and chronic obstructive lung disease (COPD). We developed a Pulmonologist-led Chronic Lung Disease Program (CLDP) for patients with severe asthma and COPD and analyzed its impact on healthcare utilization and predictors of its effectiveness.
Methods: CLDP elements included clinical evaluation, onsite pulmonary function testing, health education, and self-management action plan along with close scheduled and on-demand follow-up. Patients with $\geq$2 asthma or COPD exacerbations requiring emergency room visit or hospitalization within the prior year were enrolled, and followed for respiratory related ER visits (RER) and hospitalizations (RHA) over the year (357 $\pm$ 43 days) after CLDP interventions.
Results: A total of 106 patients were enrolled, and 104 patients were subject to analyses. During the year of follow-up after CLDP enrollment, there was a significant decrease in mean RER

Abbreviations: All-ER, all cause emergency room visits; All-HA, all cause hospitalizations; BNP, Brain Natriuretic Peptide; CHF, congestive heart failure; CLDP, Chronic Lung Disease Program; COPD, chronic obstructive lung disease; FEV1, forced expiratory volume in first second; GERD, gastroesophageal reflux disease; ICS, inhaled corticosteroids; LAMA, long acting antimuscarinic agents; LABA, long acting beta agonists; LOS, length of stay; RER, respiratory related emergency room visits; RHA, respiratory related hospitalizations; RV, residual volume; TLC, total lung capacity.

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(0.56 ± 1.48 versus 2.62 ± 2.81, $p < 0.0001$), mean RHA (0.39 ± 0.08 versus 1.1 ± 1.62, $p < 0.0001$), and 30 day rehospitalizations (0.05 ± 0.02 versus 0.28 ± 0.07, $p < 0.0001$). Reduction of healthcare utilization was strongly associated with GERD and sinusitis therapy, and was independent of pulmonary rehabilitation. Direct variable cost analyses estimated annual savings at $1.17 million. Multivariate logistic regression analysis revealed lack of spirometry utilization as an independent risk factor for severe exacerbations.

Conclusions: A Pulmonologist-led disease management program integrating key elements of care is cost effective and significantly decreases severe exacerbations. Integrated programs should be encouraged for care of frequent exacerbators of asthma and COPD.

Introduction

Asthma and COPD affect an estimated 64 million and 235 million people respectively, worldwide [1—3]. While COPD alone accounts for nearly 800,000 hospitalizations and estimated $50 billion in healthcare expenditures, asthma adds another $56 billion in healthcare costs [1,3]. Given the significant drain of healthcare resources from severe obstructive lung disease, the Centers for Medicare and Medicaid Services have specified financial penalties for hospitals; directed towards rehospitalization after COPD exacerbations as part of the Hospital Readmissions Reduction Program [4].

Several interventions have been studied independently to reduce healthcare utilization in COPD [4]. Few studies have investigated combined interventions for obstructive lung disease in the setting of an integrated disease management program. There is however significant heterogeneity in the reported components of the program; and lack of structured program outline that can be adopted in practice [5]. Recent data investigating disease management programs have reported conflicting outcomes. Rice et al. implemented a simple program using disease education by a respiratory therapist combined with an action plan, and reported reduced hospitalization and ED visits in patients with severe COPD [6]. In contrast, Fan et al. implemented disease education by case managers combined with an action plan, and reported excess mortality in the intervention group [7]. The trial was aborted prematurely due to elevated all-cause mortality in the intervention group and found no difference in the hospitalization rates. Consequently, a recent systematic review concluded that the evidence base is inadequate to recommend specific interventions to reduce rehospitalizations after COPD exacerbations [4]. Similarly, studies investigating self-management interventions are heterogeneous and its most effective form and content remain unclear [8]. For severe asthma, data on role of disease management programs are limited to none [9—11]. Irrespective, recurrent exacerbations significantly increase both mortality and morbidity in severe obstructive lung disease; accounting for substantial healthcare utilization [5,12—14]. Hence, we sought to determine the impact of an integrated multidisciplinary program incorporating interventions of proven benefit on healthcare utilization in severe obstructive lung disease. We report here significant associations and predictors of program success.

Methods

Chronic Lung Disease Program

We modeled a Chronic Lung Disease Program (CLDP) in May 2013 at the Community Regional Medical Center, a 600 bed community-based academic hospital affiliated with the UCSF School of Medicine (see Fig. 1). CLDP comprised of a nurse practitioner, respiratory therapist and health educator that were dedicated full-time to the program. Social workers and medical assistants assisted with clinic work-flow. Case managers monitored patients hospitalized for asthma and COPD exacerbations to facilitate transition into the CLDP. Elements of care included: clinical evaluation by nurse practitioner, independent face-to-face visit for health education (asthma triggers, breathing and inhaler use techniques), action plan teaching by respiratory therapists, onsite pulmonary function testing, psychosocial assessment by social worker, and referrals to Smoking Cessation and Pulmonary Rehabilitation programs. Initial visit ranged from 60 min to 120 min, while follow-up visits ranged from 20 min to 45 min. On-demand "walk-in" visits were allowed for enrolled patients. Program policies and education content were developed and directly supervised by a Pulmonologist, dedicating an average of 4—8 hours per week. Obstructive lung disease evaluation and therapy was based on severity and in accordance with current asthma and COPD treatment guidelines [15,16].

Study design and data collection

Referrals were obtained from inpatient and emergency room. Enrollment criteria specified patients above 18 years of age with physician diagnosed asthma or COPD; and with two or more exacerbations that required ER visits or Hospitalizations in the 12 months prior to referral. All patients received CLDP interventions and were followed prospectively for 1 year (after program enrollment) for respiratory related emergency room visits (RER) or respiratory related hospitalizations (RHA), where the primary diagnosis was related to an exacerbation of asthma or COPD. All cause (irrespective of the presenting complaint or primary diagnosis) emergency room visits (All-ER) and hospitalizations (All-HA) were monitored. ER visits and hospitalizations over the year prior to program enrollment were assessed via

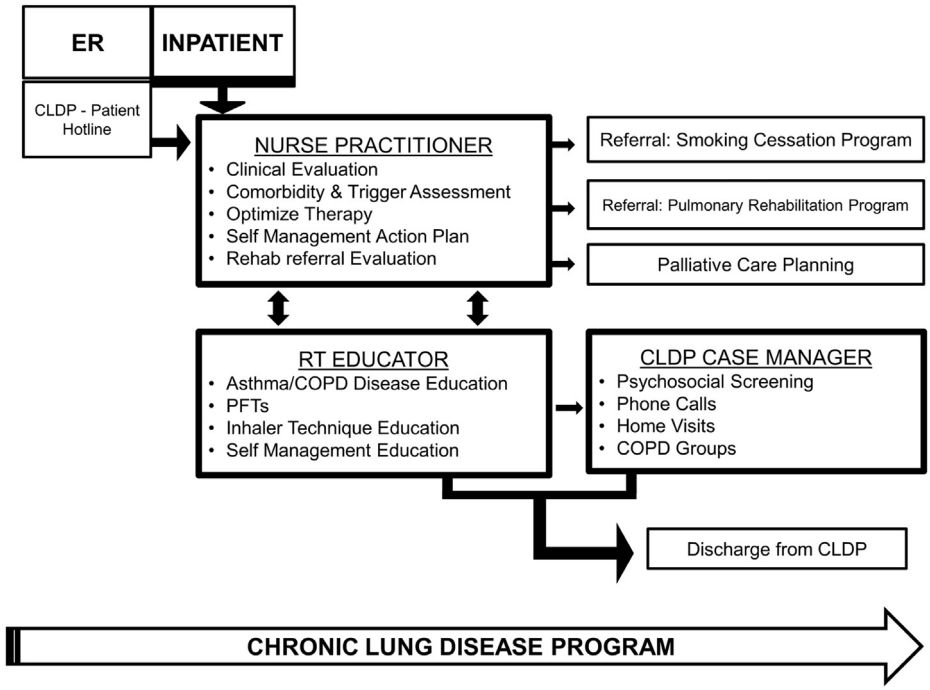

Figure 1 Pulmonologist-led integrated lung disease program model.

retrospective chart review and hospital records. Demographics, risk factors, respiratory medication usage, and diagnostic data in the 12 months prior to and after enrollment in the CLDP were collected and entered into a secured database for analyses. Study was reviewed and approved by the Institutional review board committee of the Community Medical Centers (IRB approval #2013077).

Analyses

Sample size power calculations: We hypothesized that the mean RER and RHA would decrease by 30% post CLDP interventions. Assuming a statistically significant change in the mean RER and RHA, and using a one-sided paired *t* test at a significance level of 0.025 and 80% power; the required sample size was calculated to be 80 patients. We chose to enroll a minimum of 100 patients.

Statistical analyses were conducted (*SPSS software*, *Version 22*, *IBM*) to compare means of annual visits using paired sample *t*-test. Univariate analyses were performed to determine associations of independent interventions (pre and post-program enrollment) with effectiveness of the program in reducing healthcare utilization. Chi-square tests were used for exact measures of association. A two-sided Fisher exact *p*-value is reported for all intervention analyses. A *p*-value of <0.05 was considered significant for all analyses. Multivariate binary logistic regression analyses were performed to determine independent predictors of effectiveness of CLDP.

Cost analysis: Patients were assigned costs based on the relative resource consumption of each visit. For these analyses, variable costs were used to evaluate any potential cost savings. By taking the variable costs assigned to these patients via charge codes, the total variable cost per encounter was evaluated. Within this study, the variable costs were composed of salaries (75%), supplies (12%), drugs (6%), and miscellaneous other expenses (7%). The relative percentages of these costs did not vary significantly between each of the encounter types (ER versus inpatient), nor did they change significantly between periods (Pre and Post CLDP enrollment).

Results

Baseline characteristics

One hundred and six patients with severe asthma and COPD (meeting enrollment criteria) were enrolled over 3 months (May through July of 2013) into CLDP, and followed for a mean of 357 $\pm$ 43 days following enrollment. Two patients withdrew from the program during this time and were excluded from the analyses. There were total of three deaths during the year of follow up. All three patients (mean forced expiratory volume in first second (FEV1) of 1.3 L, 43% predicted) had been subject to CLDP palliative interventions and enrolled in hospice care with eventual death (day 56, day 197 and day 315 after enrollment). Baseline characteristics of the 104 patients subject to analysis are shown in Table 1. There were 53 patients with asthma (and 51 patients with COPD) with a baseline FEV1 of 1.92 $\pm$ 0.81 L, and mean residual volume (RV) of 146 $\pm$ 51% of the predicted value along with a mean RV/TLC (Total Lung capacity) ratio of 47 $\pm$ 12. Patients had a mean of 3.75 $\pm$ 3.64 asthma or COPD exacerbations (requiring ER visit or hospitalization) in the year prior to enrollment. Thirty eight of the 104 patients were active smokers. Major co-morbidities included history of sinusitis, gastroesophageal reflux disease (GERD), and hypertension in 79%, 61%

Table 1 Baseline characteristics.

Characteristic	# Patients (%)	Mean ± SD
Age (years)	104	54 ± 12
Gender		
Male	50 (48%)	
Female	54 (52%)	
Ethnicity		
African American	21 (20%)	
Caucasian	33 (32%)	
Hispanic	41 (40%)	
Other (non-hispanic)	9 (8%)	
BMI		33 ± 10
Obstructive lung disease		
Asthma	53 (51%)	
COPD	51 (49%)	
FEV1 — L (percent predicted)	104	1.92 ± 0.81 (64% ± 23%)
RV — L (percent predicted)	104	2.8 ± 1.22 (146% ± 51%)
RV/TLC ratio	104	47 ± 12
Co-morbidities		
H/o sinusitis	82 (79%)	
H/o GERD	63 (61%)	
H/o hypertension	61 (59%)	
H/o DM	22 (21%)	
H/o OSA	19 (18%)	
H/o CHF	13 (13%)	
BNP (patients without H/o CHF)	67 (74%)	35 ± 45
Smoking status		
Current	38 (37%)	
Nonsmokers (or former)	66 (63%)	
Pulmonary exacerbations (per year)	104	3.75 ± 3.64
Insurance		
MISP (county)	49 (47%)	
Contract insurance	17 (17%)	
Medical	18 (17%)	
Medicare	20 (19%)	

and 59% of patients respectively. Only 13 of the 104 patients had a history of congestive heart failure (CHF). In patients without history of CHF, mean baseline Brain Natriuretic Peptide (BNP) was 35 ± 45 (BNP could not be obtained in 24 patients). All patients had some form of insurance with 47% of the patients insured through the Fresno County (MISP, medically indigent services program).

Effect on healthcare utilization

There were a total of 281 RER and 123 RHA in the 12 months prior to program enrollment (Pre-CLDP). Over the 12 months after enrollment and intervention in the CLD Program, these were reduced to 60 RER and 48 RHA. Similarly, all-cause ER visits and hospitalizations were also significantly reduced (499 All-ER visits and 149 All-HA pre-CLDP, versus 239 All-ER and 105 All-HA post-CLDP, see Fig. 2). There was a statistically significant reduction in the mean ER visits and hospitalizations for both respiratory related and all-cause events (see Table 2). The mean 30-day respiratory related re-hospitalizations were significantly reduced post-CLDP (0.28 versus 0.05, $p < 0.0001$). Despite reduction in overall hospitalization and readmission rates, there was a statistically significant increase in the mean length of stay (LOS) for admissions post-CLDP. There was a statistically insignificant improvement in the mean FEV1 ($n = 48$) by 40 ml over the 12 months after CLDP enrollment.

Effect on variable costs

Total variable costs over the 12 months prior to CLD program enrollment were $435,528 for inpatient hospitalizations (RHA) and $107,728 for RER visits for the hundred and four patients enrolled in that quarter of the year. After CLD program interventions, these costs were significantly reduced to $212,885 for RHA and $36,817 for RER. This reflected a quarterly total cost savings of $293,555 (See Table 2).

Associations and predictors of effectiveness

We analyzed differences in independent interventions pre and post CLDP enrollment to determine the associations with impact of the CLD program using univariate analyses (see Table 2). Spirometry utilization, therapy with long acting antimuscarinic agents (LAMA) and long acting beta agonists (LABA) was significantly improved post-CLDP. There was no statistically significant difference in inhaled corticosteroids (ICS) and home oxygen therapy use post-CLDP. Therapy of comorbidities (GERD and Sinusitis therapy) was also significantly improved post-CLDP. About 10% of the patients were referred to and successfully completed pulmonary rehabilitation program. Multivariate binary logistic regression analyses revealed Spirometry utilization in the CLD program to be an independent predictor of decreased respiratory related ER visits (but not for RHA,

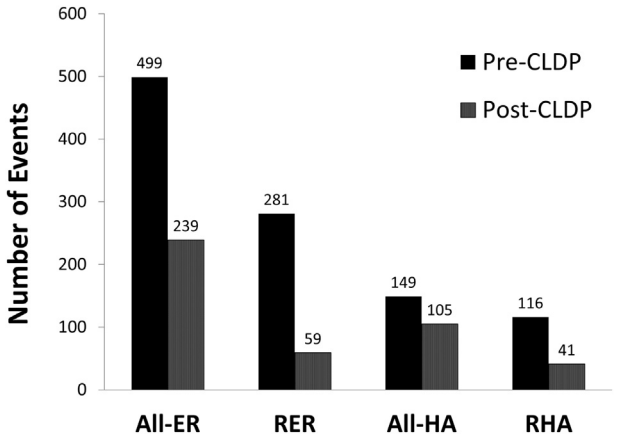

Figure 2 Effect of CLD program on healthcare utilization: respiratory related ER visits (RER) and hospitalizations (RHA), all cause ER visits (All-ER) and hospitalizations (All-HA) in the 12 months prior to (Pre-CLDP) and 12 months after enrollment in CLDP (Post-CLDP). All changes were statistically significant ($p < 0.01$).

Table 2 CLD program outcomes and associations of independent interventions.

Outcomes	Pre-CLDP	Post-CLDP	*p* value
RER (mean visits ± SD)	2.62 ± 2.81	0.56 ± 1.48	<0.0001
RHA (mean hospitalizations ± SD)	1.10 ± 1.62	0.39 ± 0.08	<0.0001
All-ER (mean visits ± SD)	4.75 ± 5.45	2.25 ± 3.46	<0.0001
All-HA (mean hospitalizations ± SD)	1.40 ± 2.13	1 ± 2.05	0.034
FEV1 (mean ± SD)	1.78 ± 0.80	1.82 ± 0.77	0.445
Length of stay (mean days ± SD)	3.21 ± 2.57	4.06 ± 3.62	<0.0001
30 Day re-admits (mean admissions ± SD)	0.28 ± 0.07	0.05 ± 0.02	<0.0001
Quarterly total direct costs: (RER/RHA, dollars)	$543,256	$249,701	
Interventions			
Spirometry utilization (# patients with spirometry)	39 (38%)	101 (97%)	<0.0001
LABA (# patients treated)	75 (72%)	93 (89%)	<0.005
LAMA (# patients treated)	37 (36%)	70 (67%)	<0.0001
ICS (# patients treated)	86 (83%)	94 (90%)	0.154
GERD therapy (# patients treated)	39 (38%)	77 (74%)	<0.0001
Sinusitis therapy (# patients treated)	32 (31%)	88 (85%)	<0.0001
Home oxygen therapy (# patients treated)	18 (17%)	21 (20%)	0.72
Referral pulmonary rehabilitation (# completed)	1 (1%)	10 (10%)	<0.01

AER or AHA), when controlled for LABA, LAMA, GERD and sinusitis therapy (Odds ratio 2.94, 95% confidence interval 1.03–8.4, $p = 0.024$, see Table 3).

All associations and reduction in parameters of healthcare utilization (RER, RHA, AER, AHA) were independent of Pulmonary rehabilitation (analyses remained statistically significant with $p < 0.05$, when excluding patients subject to pulmonary rehabilitation, $n = 10$).

Discussion

Our data suggest that a Pulmonologist-led integrated program that integrates evidence based interventions (rather than in isolation); effectively reduces preventable emergency room visits and hospitalizations. To our knowledge, this is the first report analyzing associations and predictors of success of an integrated program targeted for asthma and COPD. It is not surprising that a dedicated multidisciplinary approach might be necessary for severe asthma and COPD, both of which are thought to be complex polygenic diseases with multiple triggers and co-morbidities. We were encouraged to find that utilization of Spirometry which is widely recommended but poorly practiced, emerged as an independent predictor of reduction in exacerbations of asthma and COPD.

Reducing healthcare utilization in patients with severe obstructive lung disease is currently a topic of interest. Recurrent exacerbations and hospitalizations not only increase mortality but also independently cause an accelerated decline in the FEV1 [17,18]. In addition, hospitalizations cost more than any other component of care for asthma and COPD [3,19,20]. Having a history of prior exacerbation was found to be the single most important predictor of future exacerbations across all stages of severity of COPD [21]. In our integrated program model, we found a significant decrease in ER visits and hospitalizations. There was however an increase in the LOS suggesting that patients who do get hospitalized despite CLDP interventions likely had more severe exacerbations with increased LOS. Close follow-up and health education in a clinical setting may be required for successful use and timely initiation of a self-triggered action plan. In addition to scheduled follow up soon after administering a self-triggered action plan, CLDP patients were provided direct telephonic access during and after hours. This provides a better understanding and execution of the disease therapy and action plan, thereby decreasing preventable ER visits and hospitalizations while allowing for seeking of emergency care when in fact necessary.

Spirometry was underutilized in our study population prior to enrollment in CLD program (less than 40% of patients had completed Spirometry pre-CLDP). These data are consistent with prior reports of spirometry underutilization [22]. Utilization of spirometry independently predicted decrease in severe exacerbations requiring ER visits in our study cohort. These data suggest that establishing universal spirometry utilization for all patients with asthma and COPD must be an integral part of any program targeting reduction in exacerbations. Lack of spirometry utilization may contribute to not only a lack of recognition of severity of disease and need for step-up therapies, but may also mask other comorbidities and triggers. Most patients with severe asthma and COPD exacerbations have been reported to have multiple comorbidities and triggers [11,20,23,24]. A significant proportion of patients in our cohort had GERD

Table 3 Predictors of reduced respiratory ER visits.

Variable	Odds ratio	95% CI	*p* value
Spirometry utilization	2.94	1.03–8.40	0.024*
LABA therapy	1.52	0.36–6.42	0.57
LAMA therapy	0.5	0.18–1.41	0.28
GERD therapy	0.48	0.16–1.44	0.29
Sinusitis therapy	1.84	0.54–6.20	0.50

*$p < 0.05$.

and sinusitis. Optimizing therapy of GERD and sinusitis was strongly associated with reduction of healthcare utilization in our study. This is in accord with recent data implicating GERD as an independent risk factor for increased frequency of asthma and COPD exacerbations [11,25]. Taken together, these data suggest that frequent exacerbators should be aggressively evaluated and treated for comorbidities and triggers, specifically GERD and sinusitis. Only 13% of our cohort had a history of congestive heart failure, even though 59% had a known history of hypertension. A low BNP value in majority of the others suggested that the prevalence of heart failure in our cohort was fairly low. It is perhaps more beneficial to incorporate interventions in a program that are targeted towards identification and therapy of patient specific comorbidities, when present; rather than to structure disease-specific interventions solely.

Recent guidelines and evidence suggest that patients with frequent exacerbations may benefit from use of LAMA in both asthma and COPD [16,26]. Addition of LAMA therapy to ICS and LABA therapy (triple therapy) has been shown to reduce exacerbations and improve quality of life in patients with COPD [27]. In our study, we found a strong association of LAMA (but not ICS) therapy with reduction of healthcare utilization. Referral to pulmonary rehabilitation program also showed a strong association with reduction in healthcare utilization, as expected. Despite well-established effectiveness of pulmonary rehabilitation in reducing COPD exacerbations, poor referral patterns prevail even in patients with severe exacerbations. An integrated program can be expected to improve uptake of existing guidelines for pulmonary rehabilitation.

Cost effectiveness of the CLD program was assessed using variable costs (actual costs). Billed charges are neither accurate nor reflective of actual costs, and therefore not analyzed. For the patients enrolled in one quarter, the net cost savings was $294,000 with an estimated annual cost saving of $1.17 million. Upfront costs to start such a program would include salary support for the personnel as well as space issues and associated costs. Although the initial costs may appear to be large, the downstream benefits from reduction of resource utilization cannot be underestimated.

Our study has several limitations. Inherent to the retrospective cohort study design, it lacks a control group. The sample size is relatively small, and long term outcomes beyond a year were not assessed. Congestive heart failure was under-represented in our cohort limiting generalizability to patients with co-existent heart failure. Also, our obstructive lung disease cohort included both asthmatics and COPD patients into the study. We structured the program incorporating evidence based strategies that address unmet needs of frequent exacerbators of severe obstructive lung disease (both asthma and COPD), with subsequent disease specific care dictated by current guidelines [15,16]. This allowed for inclusion of exacerbators of both severe asthma and COPD; phenotypic differentiation of which can at times be challenging for the generalist as well as the specialist. Furthermore, recent data have described an asthma-COPD overlap phenotype in about 15—20% of patients with obstructive lung disease (and upto 50% in patients over age 50 years) [28,29]. Interestingly, patients with features of both asthma and COPD have been reported to have increased disease severity and exacerbations [30]. While specific interventions vary for severe asthma and COPD, we believe that the key components of care in our CLDP model are likely to benefit patients with both diseases. For an integrated program model with an eventual goal of delivering high-quality holistic care and thereby reducing healthcare utilization, a broad patient-centered approach encompassing frequent exacerbators of both asthma and COPD seems reasonable. A particular strength of our study is the robust program structure that included a dedicated nurse practitioner directly supervised by a Pulmonologist. We also report data on predictors of success and a cost-effectiveness analysis for our model. Cost analyses did not include costs to set up a pulmonary rehabilitation program; our CLDP model assumes access to an independent pulmonary rehabilitation program. While encouraging, our data should be regarded as a pilot study which needs further confirmation in a larger randomized controlled trial with a longer duration of follow up.

In summary, our study demonstrates the effectiveness of an integrated disease management program modeled for care of patients with recurrent exacerbations of severe asthma and COPD. Besides reducing preventable exacerbations, it may optimize continuity and transition of care post-hospitalization by providing a medical home for patients with both diseases. Further, it may improve utilization of spirometry and pulmonary rehabilitation programs. Pulmonologist-led integrated disease management programs should be promoted in the care of frequent exacerbators of asthma and COPD.

Conflict of interest

All authors report no conflict of interest.

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References

[1] http://www.cdc.gov/asthma/impacts_nation/asthmafactsheet.pdf, [accessed 12.06.14].
[2] Mannino DM, Buist AS. Global burden of COPD: risk factors, prevalence, and future trends. Lancet 2007;370:765—73.
[3] Miller JD, Foster T, Boulanger L, et al. Direct costs of COPD in the U.S.: an analysis of Medical Expenditure Panel Survey (MEPS) data. COPD 2005;2:311—8.
[4] Prieto-Centurion V, Markos MA, Ramey NI, et al. Interventions to reduce rehospitalizations after chronic obstructive

pulmonary disease exacerbations. A systematic review. Ann Am Thorac Soc 2014;11:417—24.
[5] Williams MV. A requirement to reduce readmissions: take care of the patient, not just the disease. JAMA 2013;309: 394—6.
[6] Rice KL, Dewan N, Bloomfield HE, et al. Disease management program for chronic obstructive pulmonary disease: a randomized controlled trial. Am J Respir Crit Care Med 2010;182: 890—6.
[7] Fan VS, Gaziano JM, Lew R, et al. A comprehensive care management program to prevent chronic obstructive pulmonary disease hospitalizations: a randomized, controlled trial. Ann Intern Med 2012;156:673—83.
[8] Zwerink M, Brusse-Keizer M, van der Valk PD, et al. Self management for patients with chronic obstructive pulmonary disease. Cochrane Database Syst Rev 2014;3:CD002990.
[9] Andrews KL, Jones SC, Mullan J. Asthma self management in adults: a review of current literature. Collegian 2014;21: 33—41.
[10] Kenyon CC, Melvin PR, Chiang VW, et al. Rehospitalization for childhood asthma: timing, variation, and opportunities for intervention. J Pediatr 2014;164:300—5.
[11] ten Brinke A, Sterk PJ, Masclee AA, et al. Risk factors of frequent exacerbations in difficult-to-treat asthma. Eur Respir J 2005;26:812—8.
[12] Hasegawa K, Tsugawa Y, Tsai CL, et al. Frequent utilization of the emergency department for acute exacerbation of chronic obstructive pulmonary disease. Respir Res 2014;15:40.
[13] Soler-Cataluna JJ, Martinez-Garcia MA, Roman Sanchez P, et al. Severe acute exacerbations and mortality in patients with chronic obstructive pulmonary disease. Thorax 2005;60: 925—31.
[14] Suissa S, Dell'Aniello S, Ernst P. Long-term natural history of chronic obstructive pulmonary disease: severe exacerbations and mortality. Thorax 2012;67:957—63.
[15] GINA. Global strategy for asthma management and prevention. 2012. http://www.ginasthma.org/local/uploads/files/GINA_Report_March13_1.pdf [accessed May 2013].
[16] GOLD GIfCOLD. Global strategy for the diagnosis, management, and prevention of chronic obstructive lung disease. 2011. http://www.goldcopd.org/guidelines-global-strategy-for-diagnosis-management.html [accessed May 2013].
[17] Donaldson GC, Seemungal TA, Bhowmik A, et al. Relationship between exacerbation frequency and lung function decline in chronic obstructive pulmonary disease. Thorax 2002;57: 847—52.
[18] Groenewegen KH, Schols AM, Wouters EF. Mortality and mortality-related factors after hospitalization for acute exacerbation of COPD. Chest 2003;124:459—67.
[19] Ivanova JI, Bergman R, Birnbaum HG, et al. Effect of asthma exacerbations on health care costs among asthmatic patients with moderate and severe persistent asthma. J Allergy Clin Immunol 2012;129:1229—35.
[20] Oostenbrink JB, Rutten-van Molken MP. Resource use and risk factors in high-cost exacerbations of COPD. Respir Med 2004; 98:883—91.
[21] Hurst JR, Vestbo J, Anzueto A, et al. Susceptibility to exacerbation in chronic obstructive pulmonary disease. N Engl J Med 2012;363:1128—38.
[22] Lusuardi M, Orlandini D. Underutilization of spirometry for the diagnosis of COPD. Chest 2008;133:313—4 [author reply 314].
[23] Ali Z, Ulrik CS. Incidence and risk factors for exacerbations of asthma during pregnancy. J Asthma Allergy 2013;6:53—60.
[24] Steppuhn H, Langen U, Scheidt-Nave C, et al. Major comorbid conditions in asthma and association with asthma-related hospitalizations and emergency department admissions in adults: results from the German national health telephone interview survey (GEDA) 2010. BMC Pulm Med 2013;13:46.
[25] Martinez CH, Okajima Y, Murray S, et al. Impact of self-reported gastroesophageal reflux disease in subjects from COPDGene cohort. Respir Res 2014;15:62.
[26] Peters SP, Kunselman SJ, Icitovic N, et al. Tiotropium bromide step-up therapy for adults with uncontrolled asthma. N Engl J Med 2010;363:1715—26.
[27] Tashkin DP, Celli B, Senn S, et al. A 4-year trial of tiotropium in chronic obstructive pulmonary disease. N Engl J Med 2008; 359:1543—54.
[28] Postma DS, Reddel HK, ten Hacken NH, et al. Asthma and chronic obstructive pulmonary disease: similarities and differences. Clin Chest Med 2014;35:143—56.
[29] Soriano JB, Davis KJ, Coleman B, et al. The proportional Venn diagram of obstructive lung disease: two approximations from the United States and the United Kingdom. Chest 2003;124: 474—81.
[30] Menezes AM, Montes de Oca M, Perez-Padilla R, et al. Increased risk of exacerbation and hospitalization in subjects with an overlap phenotype: COPD—asthma. Chest 2014;145: 297—304.