

Pulmonary rehabilitation for patients with COPD during and after an exacerbation-related hospitalization: back to the future?

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To the Editors,

The European Respiratory Society (ERS) and American Thoracic Society (ATS) guideline on Management of COPD Exacerbations was published in the *March 2017* issue of the *European Respiratory Journal* (1). Based on evidence syntheses, including meta-analyses, relevant evidence until *September 2015* was summarized, and clinical recommendations for treatment of COPD exacerbations were formulated. These Guidelines were endorsed by the ERS Executive Committee and approved by the ATS Board of Directors in December 2016.

These guidelines should provide the basis for rational decisions in the treatment of COPD exacerbations. Unexpectedly, however, this ERS/ATS Task Force made a conditional recommendation *against* the initiation of pulmonary rehabilitation during hospitalisation; and a conditional recommendation *in favour* of starting pulmonary rehabilitation within three weeks after hospital discharge. Moreover, the Task Force rated the quality of evidence for both conditional recommendations to be very low. We take the liberty to challenge these conditional recommendations as well as the assessment of the evidence relating to them. Indeed, there are multiple arguments to recommend the initiation of pulmonary rehabilitation during and (especially) directly after hospitalisation.

Patients with COPD report a broad spectrum of symptoms during exacerbations, including dyspnoea, depression, and fatigue (2), which seem to be the basis of the extreme declines in physical activity during hospitalizations (3). Additionally, comorbidities may flare up (4), and significant losses in quadriceps muscle strength (5), exercise tolerance (6) and health status occur during hospitalization (7), which only partially recover with usual care after discharge (3, 5, 8). Also, it has been shown that patients with anxiety and depression have a doubled risk of short-term hospital re-admission (9). Therefore, we strongly believe that there is a clear rationale to start early rehabilitative interventions during the exacerbation-related hospitalization in patients

with COPD, and to continue this after discharge. Importantly, the content of the integrated peri-exacerbation pulmonary rehabilitation program (which is much more than physiotherapy alone) needs to be tailored to the patient's physical and psychological status (10).

Recent randomised controlled trials (RCTs) have shown that rehabilitative interventions initiated during patients' hospital stay prevent a decline in lower-limb muscle function, balance and exercise performance, and facilitates recovery afterwards (11-15). These RCTs did not report serious adverse events. Starting early rehabilitation in the hospital setting is clearly also in line with international developments to encourage early rehabilitative interventions, which are safe and effective for patients with a spectrum of illnesses, even in mechanically ventilated, critically ill patients (16-19).

The current ERS/ATS Task Force concluded that pulmonary rehabilitation initiated during hospitalization increased mortality (1). This conclusion seems based solely on the study of Greening and colleagues, who reported a significant difference in mortality at 12 months between the rehabilitative group (starting with a median of 3 rehabilitative sessions during a median 5-day hospital stay, followed by a 6-week unsupervised home-based program, supported by telephone consultations) and the usual care control group (who did receive daily physiotherapy during hospitalization as per standard UK practice) (20). As argued previously (21), the difference in mortality began more than five months after the completion of the intervention. While of concern, the difference does not clearly relate to the early rehabilitation intervention. Indeed, the per protocol analysis did not show difference in mortality, suggesting that those who actually received the intervention were not the ones who came to harm (20). ~~Moreover, post hoc analyses showed that after statistical correction for an imbalance in the degree of airflow limitation, the increased likelihood of dying in the early rehabilitation group compared to the usual care control group loses significance (GREENING et al. ERJ 01310-2017, UNDER REVIEW).~~ Thus, it is questionable

to base a conditional recommendation against the initiation of pulmonary rehabilitation during hospitalisation on a single trial and not on the entirety of evidence. Also, it is not entirely clear how the quality of the evidence relating to this recommendation was rated by the ERS/ATS task force (1), which led to very different conclusions on the quality of the evidence compared to the recently updated Cochrane review (22).

A conditional recommendation indicates that well-informed patients may make different choices regarding whether or not to have the intervention (1). While such preference-sensitive decision making is most welcome, it should be noted, that, unfortunately, patients with COPD are mostly unaware of the value of (peri-exacerbation) pulmonary rehabilitation programs for their health outcomes (23). Moreover, our anecdotal clinical experience shows that healthcare professionals who are uneducated in pulmonary rehabilitation are already using this ERS/ATS conditional recommendation to withhold an early rehabilitative intervention in the peri-exacerbation period from patients. Indeed, during the ERS School Course on Pulmonary Rehabilitation (April 2017 in Athens, Greece), multiple concerns were expressed by participants that their local physicians read the ERS/ATS guideline on Management of COPD Exacerbations, and, in turn, did not refer for early pulmonary rehabilitation.

On December 8 2016, Puhan and colleagues published an update of their Cochrane review entitled 'Pulmonary rehabilitation following exacerbations of chronic obstructive pulmonary disease', including twenty studies, and concluded that *'Quality of life and exercise capacity were improved by rehabilitation, that the effect was substantially larger than the minimal important difference, and the quality of evidence according to GRADE was high. Results for hospital readmissions and mortality were diverse, with some studies showing that pulmonary rehabilitation reduced hospital admissions and mortality compared with usual community care (no rehabilitation), and other studies not showing such effects.'* (22). Based on the existing literature, we believe that

the ERS/ATS Task Force should have made a strong recommendation *in favour of* starting pulmonary rehabilitation in the first weeks after hospital discharge, without the conditional reservation.

To conclude, pulmonary rehabilitation ambassadors around the world have promoted pulmonary rehabilitation in patients with COPD during and shortly after an exacerbation-related hospitalization (10, 24), as this results in clinically relevant improvements in exercise performance, lower-limb muscle function, balance and quality of life compared to usual care (22). Presently, more than 75% of current pulmonary rehabilitation programs include those patients (25). Obviously, we recognize the heterogeneity of effects on mortality and hospital re-admission, which should be monitored closely. As always, the specific content of the rehabilitation intervention in the peri-exacerbation period must be tailored carefully to the patient's condition and needs. Nevertheless, given the current evidence, the basis for the ERS/ATS conditional recommendation against the initiation of PR during hospitalization is not clear. This recommendation is therefore likely to have adverse impact on the quality of care, and in turn, the physical and emotional function and quality of life of these patients. We believe this recommendation is potentially harmful for the further broadening of the scope of pulmonary rehabilitation; and sets pulmonary rehabilitation 15 years back. Therefore, we would like to encourage healthcare professionals to educate their patients and recommend pulmonary rehabilitation in the peri-exacerbation period, as only 5 to 15% of hospitalized COPD patients are currently referred for early pulmonary rehabilitation (26). The ERS and ATS should commit to undertake actions that will improve access to and pulmonary rehabilitation services for suitable patients, including those with an exacerbation-related hospitalization (24).

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References

1. Wedzicha JAEC-C, Miravittles M, Hurst JR, Calverley PM, Albert RK, Anzueto A, et al. Management of COPD exacerbations: a European Respiratory Society/American Thoracic Society guideline. *Eur Respir J*. 2017;49(3).
2. Kessler R, Stahl E, Vogelmeier C, Haughney J, Trudeau E, Lofdahl CG, et al. Patient understanding, detection, and experience of COPD exacerbations: an observational, interview-based study. *Chest*. 2006;130(1):133-42.
3. Pitta F, Troosters T, Probst VS, Spruit MA, Decramer M, Gosselink R. Physical activity and hospitalization for exacerbation of COPD. *Chest*. 2006;129(3):536-44.
4. Burt MG, Roberts GW, Aguilar-Loza NR, Quinn SJ, Frith PA, Stranks SN. Relationship between glycaemia and length of hospital stay during an acute exacerbation of chronic obstructive pulmonary disease. *Intern Med J*. 2013;43(6):721-4.
5. Spruit MA, Gosselink R, Troosters T, Kasran A, Gayan-Ramirez G, Bogaerts P, et al. Muscle force during an acute exacerbation in hospitalised patients with COPD and its relationship with CXCL8 and IGF-I. *Thorax*. 2003;58(9):752-6.
6. Carr SJ, Hill K, Brooks D, Goldstein RS. Pulmonary rehabilitation after acute exacerbation of chronic obstructive pulmonary disease in patients who previously completed a pulmonary rehabilitation program. *J Cardiopulm Rehabil Prev*. 2009;29(5):318-24.
7. Miravittles M, Ferrer M, Pont A, Zalacain R, Alvarez-Sala JL, Masa F, et al. Effect of exacerbations on quality of life in patients with chronic obstructive pulmonary disease: a 2 year follow up study. *Thorax*. 2004;59(5):387-95.
8. Donaldson GC, Wilkinson TM, Hurst JR, Perera WR, Wedzicha JA. Exacerbations and time spent outdoors in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med*. 2005;171(5):446-52.
9. Dahlen I, Janson C. Anxiety and depression are related to the outcome of emergency treatment in patients with obstructive pulmonary disease. *Chest*. 2002;122(5):1633-7.
10. Spruit MA, Singh SJ, Garvey C, ZuWallack R, Nici L, Rochester C, et al. An official American Thoracic Society/European Respiratory Society statement: key concepts and advances in pulmonary rehabilitation. *Am J Respir Crit Care Med*. 2013;188(8):e13-64.
11. Troosters T, Probst VS, Crul T, Pitta F, Gayan-Ramirez G, Decramer M, et al. Resistance training prevents deterioration in quadriceps muscle function during acute exacerbations of chronic obstructive pulmonary disease. *Am J Respir Crit Care Med*. 2010;181(10):1072-7.
12. Torres-Sanchez I, Valenza MC, Cabrera-Martos I, Lopez-Torres I, Benitez-Feliponi A, Conde-Valero A. Effects of an Exercise Intervention in Frail Older Patients with Chronic Obstructive Pulmonary Disease Hospitalized due to an Exacerbation: A Randomized Controlled Trial. *COPD*. 2017;14(1):37-42.
13. Borges RC, Carvalho CR. Impact of resistance training in chronic obstructive pulmonary disease patients during periods of acute exacerbation. *Arch Phys Med Rehabil*. 2014;95(9):1638-45.
14. Giavedoni S, Deans A, McCaughey P, Drost E, MacNee W, Rabinovich RA. Neuromuscular electrical stimulation prevents muscle function deterioration in exacerbated COPD: a pilot study. *Respir Med*. 2012;106(10):1429-34.
15. Greulich T, Nell C, Koepke J, Fechtel J, Franke M, Schmeck B, et al. Benefits of whole body vibration training in patients hospitalised for COPD exacerbations - a randomized clinical trial. *BMC Pulm Med*. 2014;14:60.
16. Burtin C, Clerckx B, Robbeets C, Ferdinande P, Langer D, Troosters T, et al. Early exercise in critically ill patients enhances short-term functional recovery. *Crit Care Med*. 2009;37(9):2499-505.
17. Zanotti E, Felicetti G, Maini M, Fracchia C. Peripheral muscle strength training in bed-bound patients with COPD receiving mechanical ventilation: effect of electrical stimulation. *Chest*. 2003;124(1):292-6.

18. Schweickert WD, Pohlman MC, Pohlman AS, Nigos C, Pawlik AJ, Esbrook CL, et al. Early physical and occupational therapy in mechanically ventilated, critically ill patients: a randomised controlled trial. *Lancet*. 2009;373(9678):1874-82.
19. Nydahl P, Sricharoenchai T, Chandra S, Kundt FS, Huang M, Fischill M, et al. Safety of Patient Mobilization and Rehabilitation in the ICU: Systematic Review with Meta-Analysis. *Ann Am Thorac Soc*. 2017.
20. Greening NJ, Williams JE, Hussain SF, Harvey-Dunstan TC, Bankart MJ, Chaplin EJ, et al. An early rehabilitation intervention to enhance recovery during hospital admission for an exacerbation of chronic respiratory disease: randomised controlled trial. *BMJ*. 2014;349:g4315.
21. Janssen DJ, Schols JM, Wouters EF, Spruit MA. One-year stability of care dependency in patients with advanced chronic organ failure. *J Am Med Dir Assoc*. 2014;15(2):127-32.
22. Puhan MA, Gimeno-Santos E, Cates CJ, Troosters T. Pulmonary rehabilitation following exacerbations of chronic obstructive pulmonary disease. *Cochrane Database Syst Rev*. 2016;12:CD005305.
23. Cox NS, Oliveira CC, Lahham A, Holland AE. Pulmonary rehabilitation referral and participation are commonly influenced by environment, knowledge, and beliefs about consequences: a systematic review using the Theoretical Domains Framework. *J Physiother*. 2017;63(2):84-93.
24. Rochester CL, Vogiatzis I, Holland AE, Lareau SC, Marciniuk DD, Puhan MA, et al. An Official American Thoracic Society/European Respiratory Society Policy Statement: Enhancing Implementation, Use, and Delivery of Pulmonary Rehabilitation. *Am J Respir Crit Care Med*. 2015;192(11):1373-86.
25. Spruit MA, Pitta F, Garvey C, ZuWallack RL, Roberts CM, Collins EG, et al. Differences in content and organisational aspects of pulmonary rehabilitation programmes. *Eur Respir J*. 2014;43(5):1326-37.
26. Jones SE, Green SA, Clark AL, Dickson MJ, Nolan AM, Moloney C, et al. Pulmonary rehabilitation following hospitalisation for acute exacerbation of COPD: referrals, uptake and adherence. *Thorax*. 2014;69(2):181-2.