ILD 환자의 증상 및 동반질환 관리

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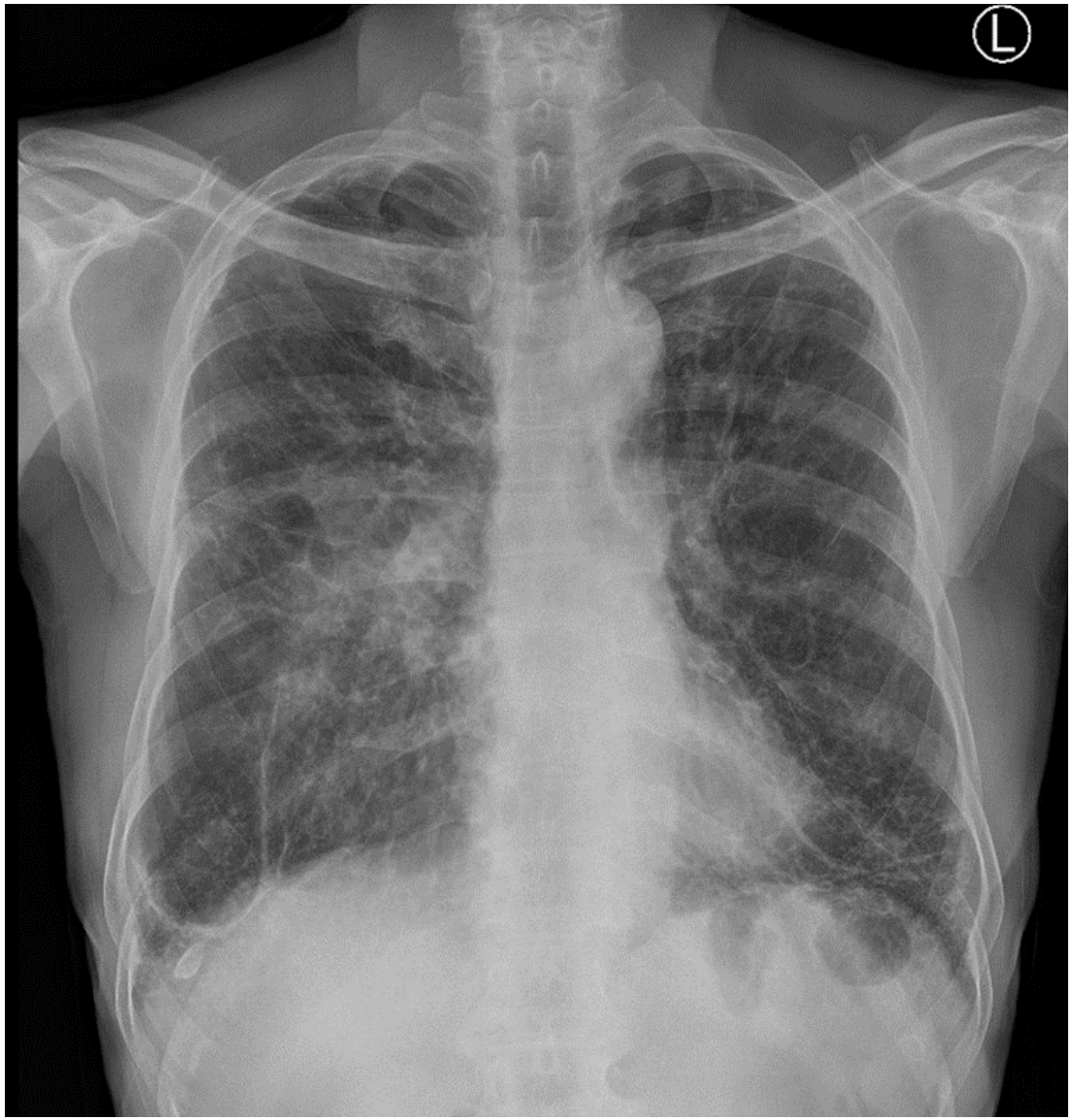
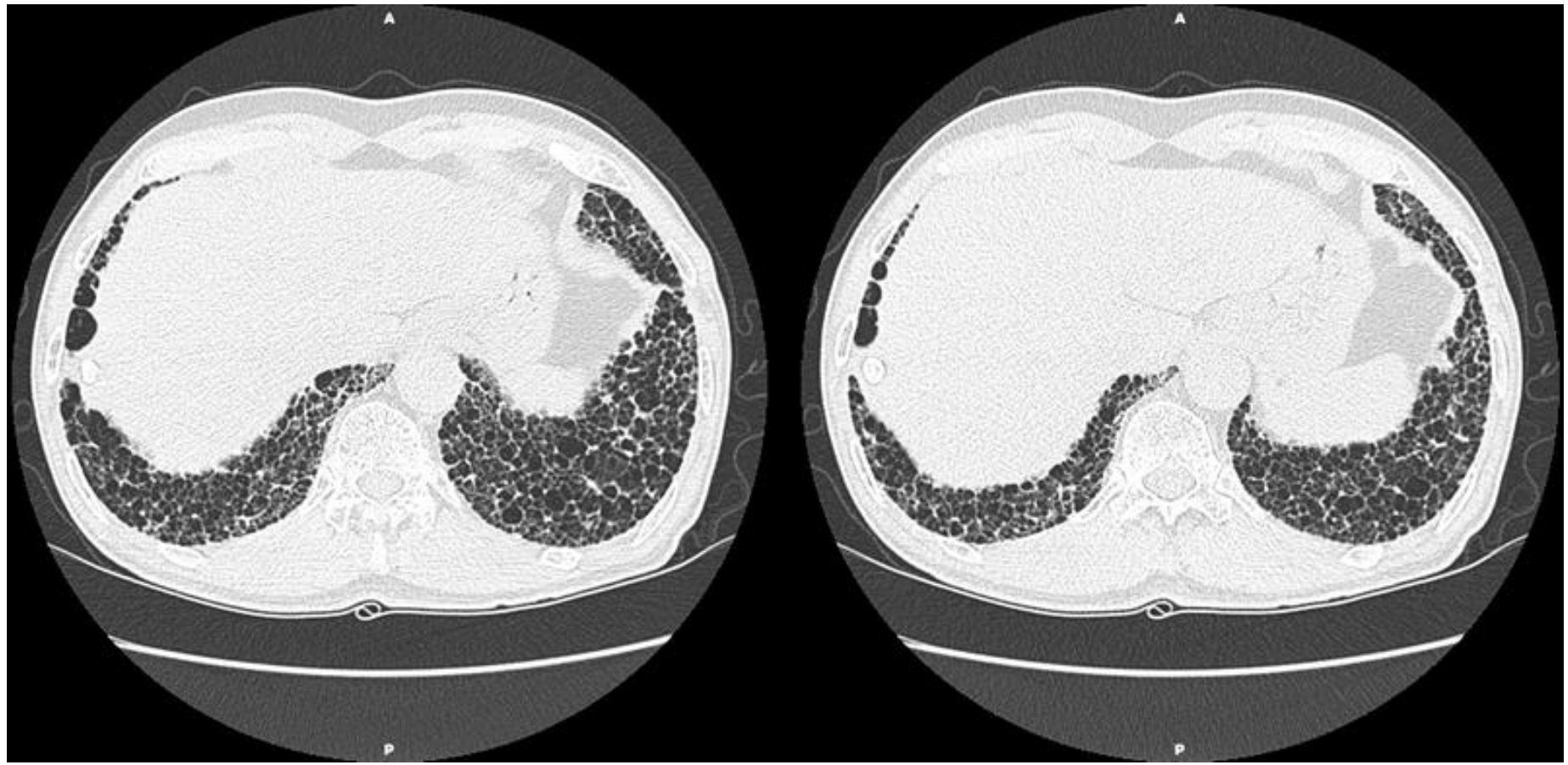
Contents

- ❖ Cough
- ❖ Dyspnea
- ❖ Gastroesophageal reflux disease
- ❖ Obstructive sleep apnea
- ❖ Sarcopenia / Frailty

증례

- 67/M
- 6개월 전부터 시작된 기침의뢰됨
  동반증상: 호흡곤란 mMRC Gr 2-3
- 과거력 : 특이 사항 없음.
- 현 흡연자: 50 갑년
- 직업력: 특이 사항 없음
- PE
  chest: inspiratory crackle in both lower thorax

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- **자가항체 검사: 특이 소견 없음**

- **FEV1/FVC ratio: 0.62**
  FEV1 (%) pred: 51.5% (1.43L)
  FVC (%) pred: 61.7% (2.3L)
- **DLCO: 50.3%**
- **6MWT: distance 305 m, 95% (resting)-> 90% (lowest)**

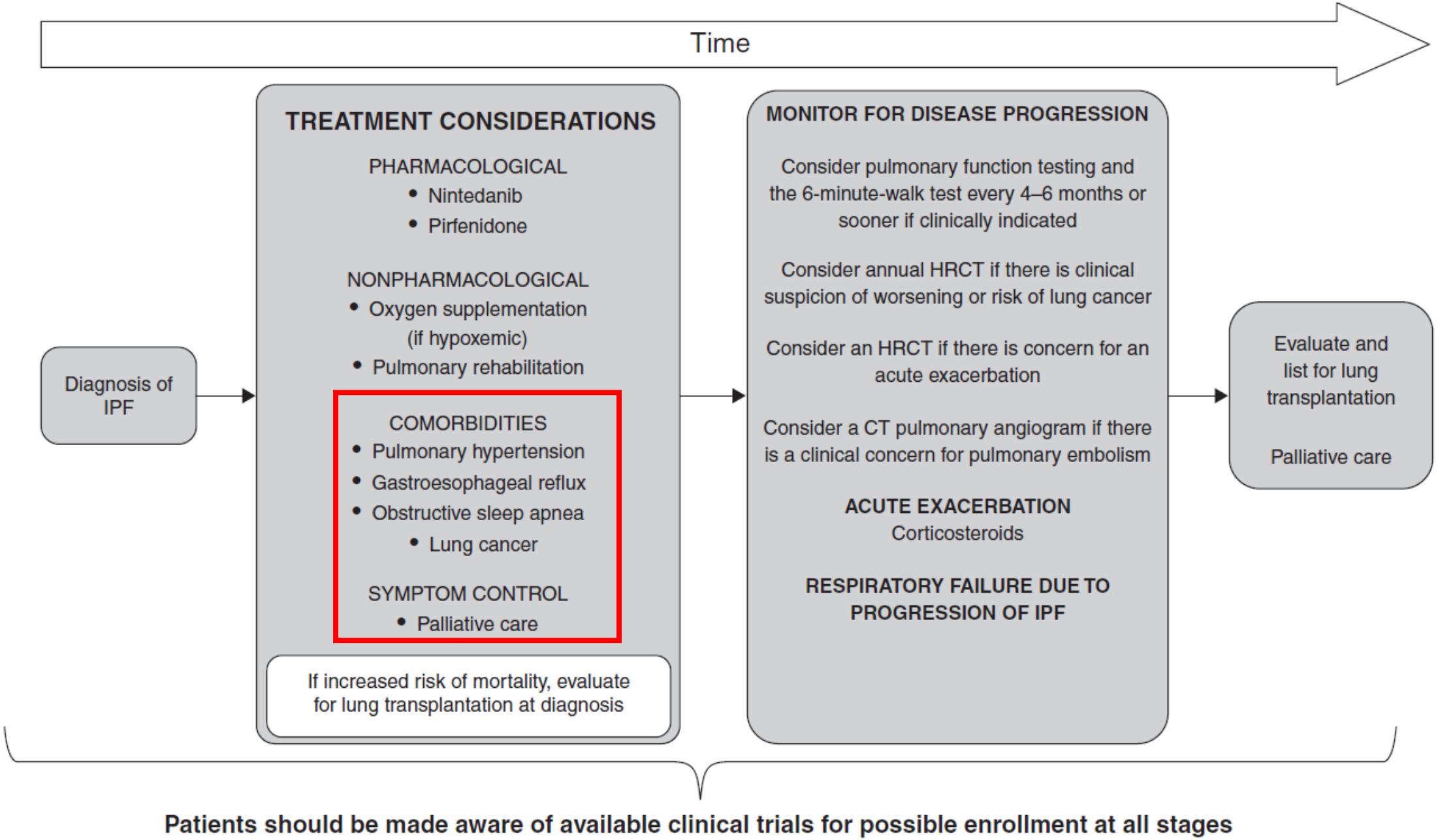
Clinical Features, Diagnosis, Management, and Outcomes of Idiopathic Pulmonary Fibrosis in Korea: Analysis of the Korea IPF Cohort (KICO) Registry

Initial Symptoms	N (%)
Asymptomatic	308 (14.4)
Dyspnea	1,112 (52)
mMRC	1.4 ± 1.0
Cough	1,077 (50.4)
Fever	36 (1.7)
Chest pain	57 (2.7)

Tuberc Respir Dis 2022; 85: 185-194

Comorbidities	Prevalence
DM	10-42% in IPF
COPD	6-67% in IPF
Gastroesophageal reflux	0–94% in IPF
Pulmonary hypertension	3-86% in IPF
Congestive heart failure	4-26% in IPF
Coronary artery disease	3-68% in IPF
Pulmonary embolism	3-6% in IPF
Lung cancer	4–23% in IPF
Obstructive sleep apnea	60–90% in IPF, 50% in SSc-ILD, 65% in sarcoidosis
Depression and anxiety	>20% in ILDs, 21-49 % in IPF

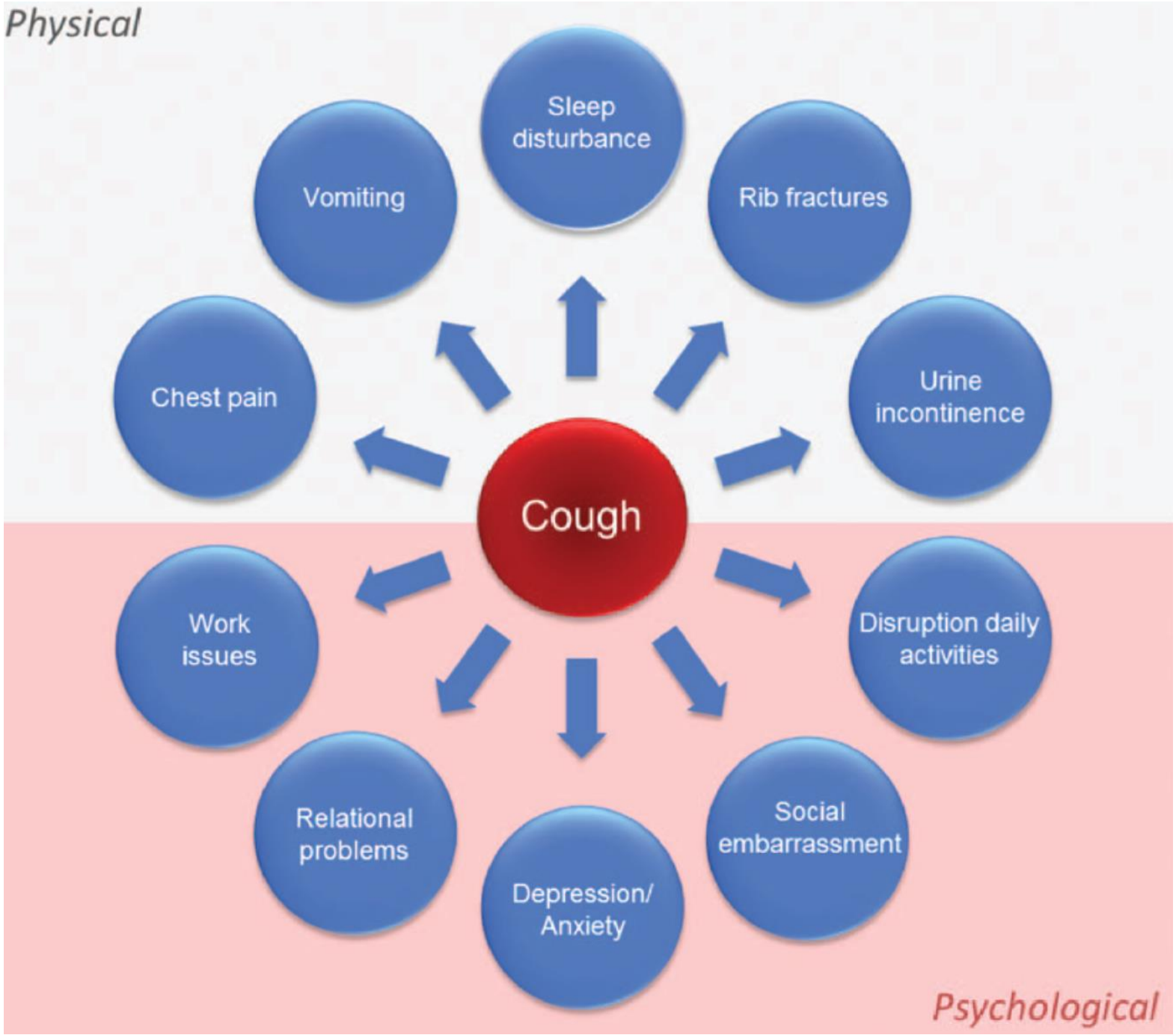
Eur Respir Rev 2017; 26: 160027
Lancet Respir Med 2017; 5: 72-84



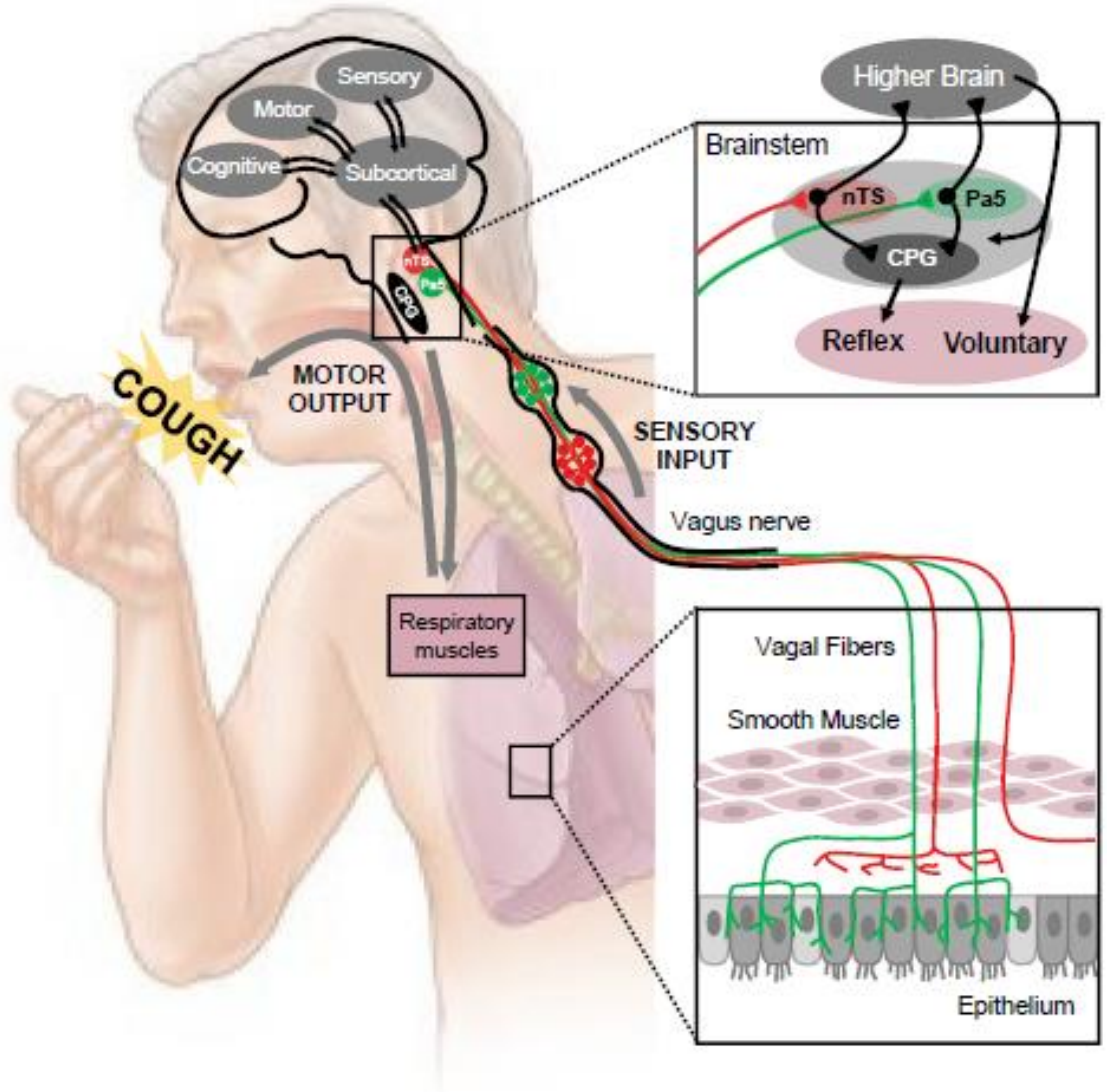
Am J Respir Crit Care Med 2022; 205: pp e18–e47

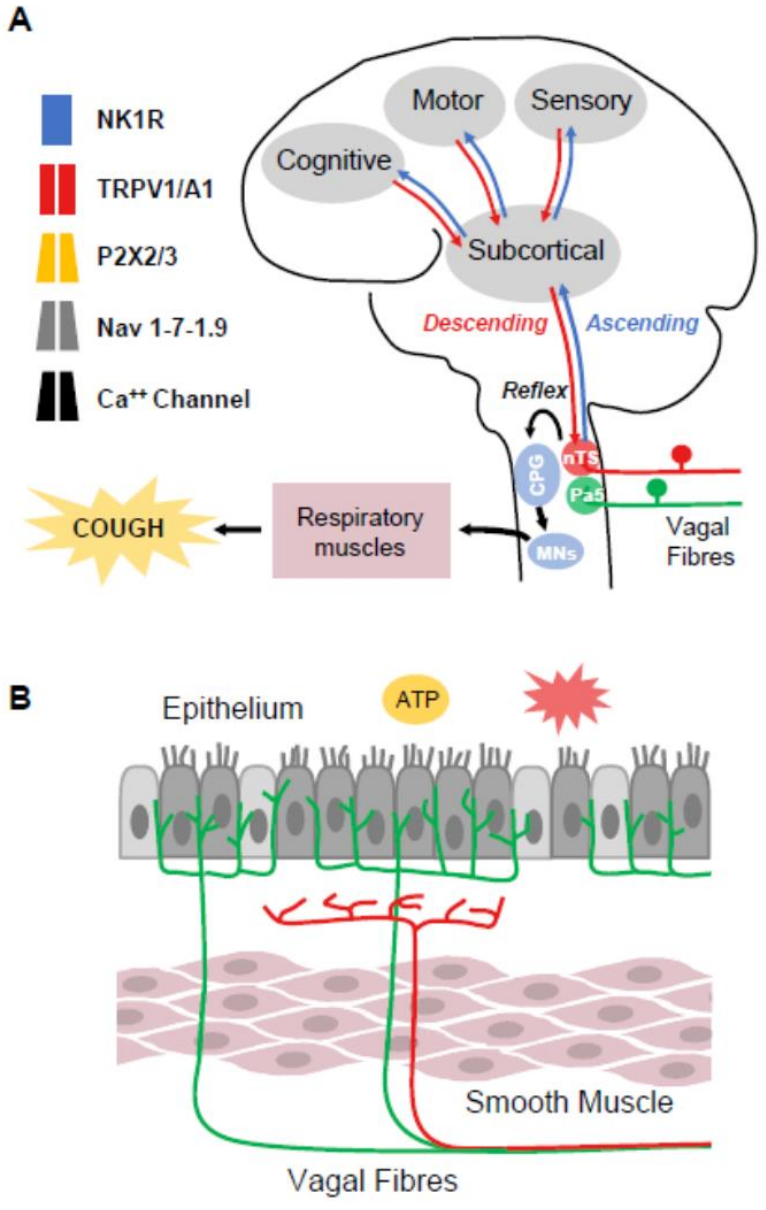
Cough

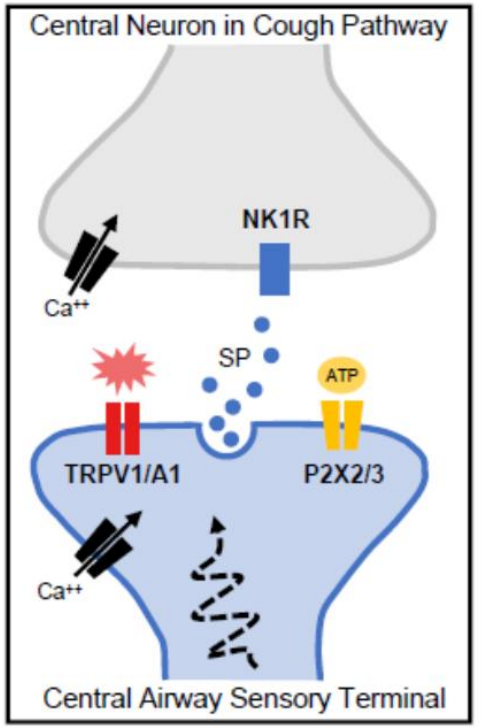
- **Common**
- **Prevalence: ～ 80%, no reliable data**
- **More in advanced form**
- **Significant impairment in quality of life and prognosis**
- **Consequence of the underlying inflammation or fibrosis**
- **Presence of a co-morbidity**

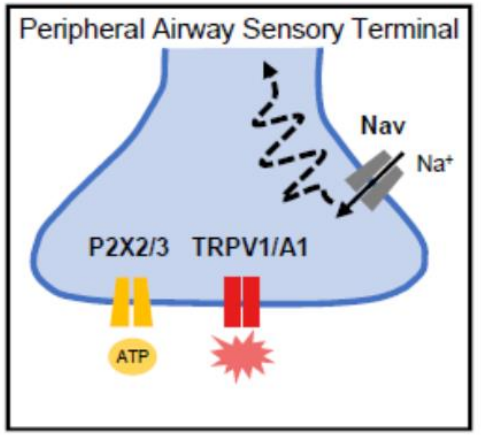


Curr Opin Support Palliat Care 2019; 13:143–151







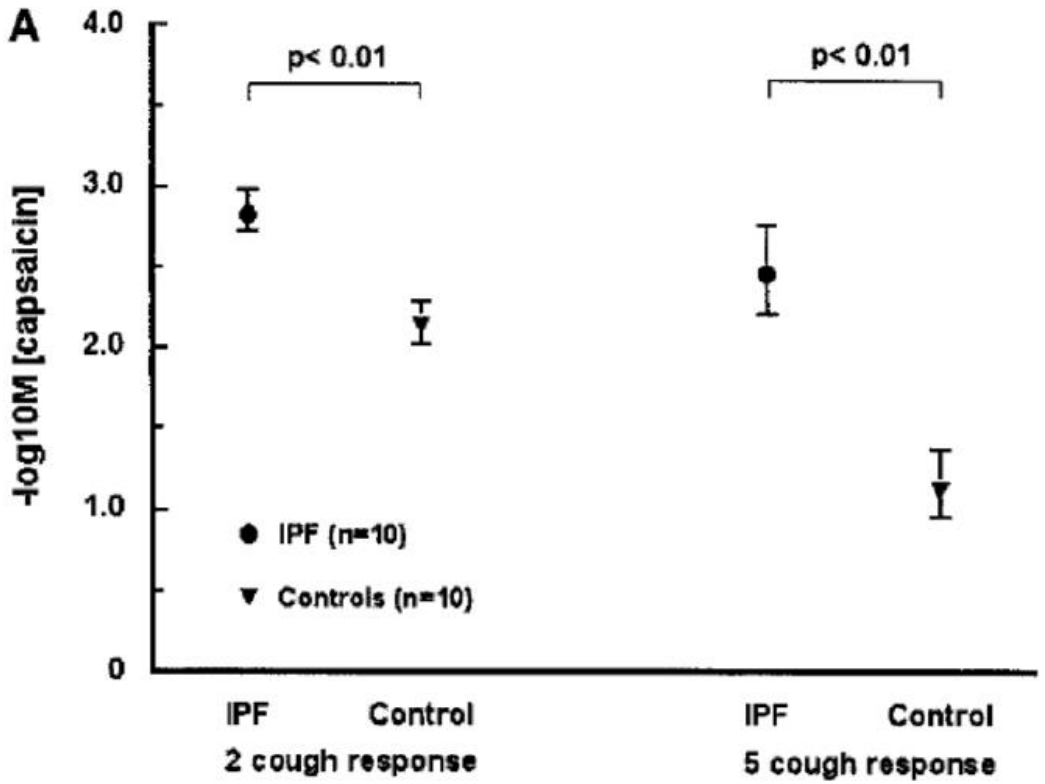


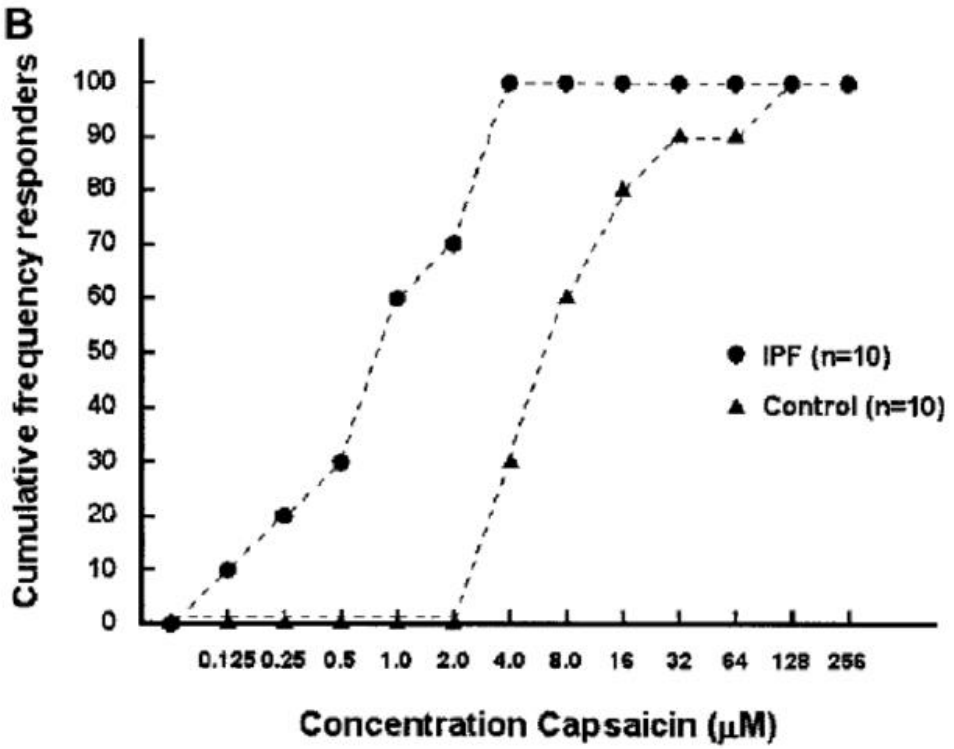
CHEST 2017; 152(4):833-841

Mechanisms

Triggers

- Smoke
- Perfumes/scents
- Throat irritation/tickle
- Noxious fumes
- Speech
- Exercise
- Cold/dry air
- Eating
- Humidity





Am J Respir Crit Care Med 2003; 168: pp 995–1002

Comorbidities

- **Cough-variant asthma**
- **Upper airway cough syndrome**
- **Gastroesophageal reflux (GERD)**
- **Obstructive sleep apnea (OSA)**
- **Medication: ACE inhibitor et al.**

TABLE 2 Cough measurements in idiopathic pulmonary fibrosis (IPF) patients

Cough measurement tool	Description	Validation studies and MCID	Advantages	Disadvantages
Subjective				
Visual analogue scale [56]	100 mm scale with extremes no cough to worst possible cough severity	Not validated in IPF	Easy to use Repeatable Responsive	Not validated in IPF or chronic cough
Cough quality-of-life questionnaire [57]	28-item cough-specific quality-of-life questionnaire with six domains	Validated in IPF (n=23) MCID in IPF: change of five points on a 28–112 scale [57]	Comprehensive questionnaire Reliable Valid instrument for assessing impact of cough	Need more studies in IPF: MCID evaluated with a retrospective anchor scale
Leicester cough questionnaire [15]	19-item self-administered chronic cough quality-of-life questionnaire with three domains	Evaluated in IPF: high correlation found with cough visual analogue scale, cough symptom score and objective cough frequency in IPF [10, 22] MCID in chronic cough: 1.3	High reliability Valid instrument for assessing impact of cough Ability to detect a response to change	Need more studies in IPF: MCID evaluated in chronic cough
Objective				
Cough challenge test [58]	Measurement of cough reflex sensitivity by inhalation of nebulised tussive agents (most common citric acid or capsaicin)	Not validated in IPF No MCID Standardised methodology published by ERS [14]	Useful for testing effect of new cough therapies on cough reflex sensitivity and for obtaining mechanistic insights	Doesn't measure efficacy of therapy or predict response in patients Limited availability
Cough monitor [59]	Microphone and recording device measuring cough in a pre-specified time slot	Validated cough monitors for chronic cough High correlation found with subjective cough measurements [10]	Measures cough frequency accurately	Currently limited to research and trails Benefit in routine clinics is not clear

Treatment of Interstitial Lung Disease Associated Cough

CHEST Guideline and Expert Panel Report

1. For patients with ILD who present with a troublesome cough, we suggest that patients be assessed for progression of their underlying ILD, or complications from immunosuppressive treatment (eg, drug side effect, pulmonary infection) and also be considered for further investigation/treatment trials for their cough according to guidelines for acute, subacute and chronic cough. (Ungraded Consensus-Based Statement)

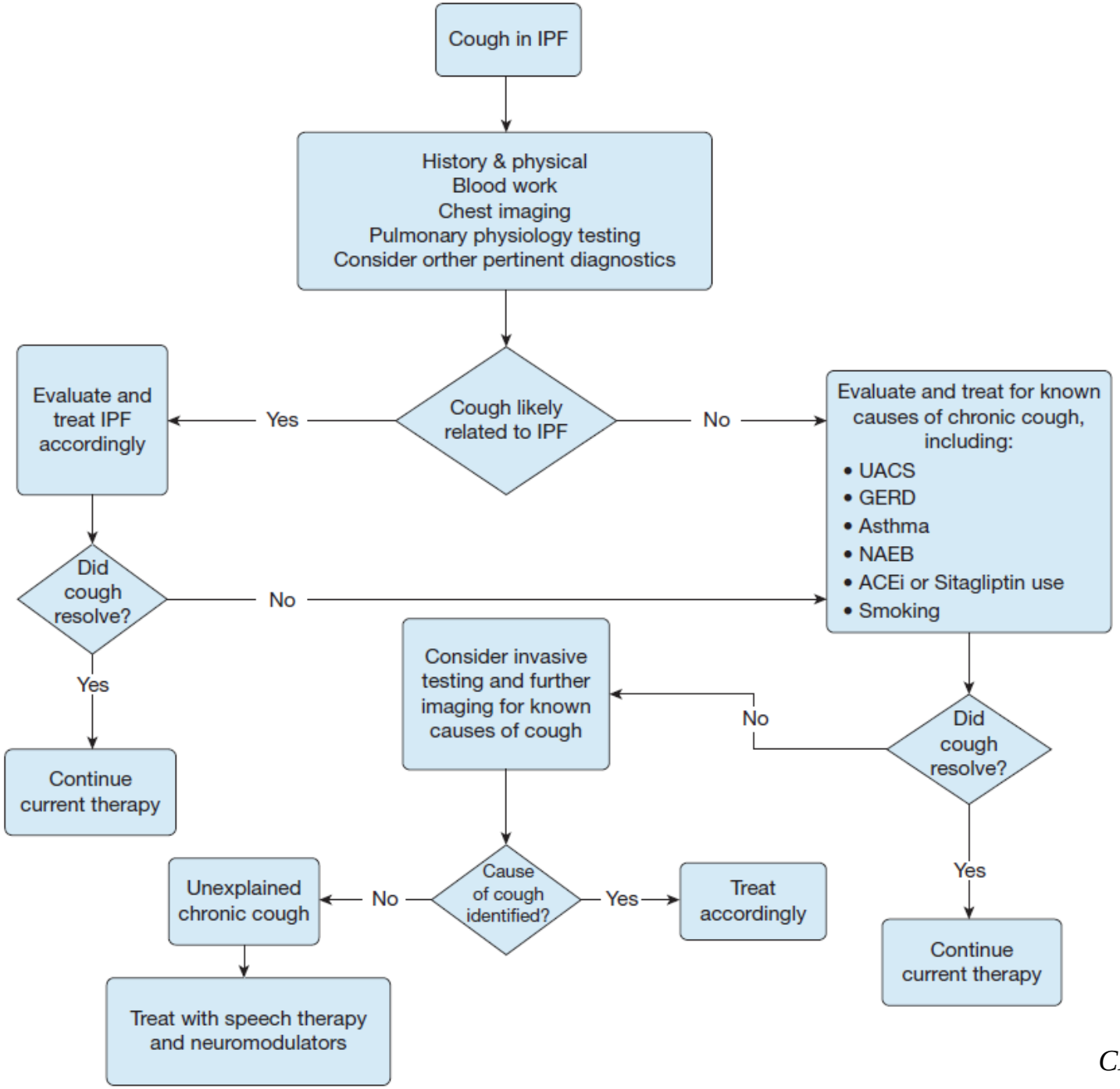
2. For patients with IPF, chronic cough and a negative workup for acid gastroesophageal reflux, we suggest that proton pump inhibitor therapy should not be prescribed. (Ungraded Consensus-Based Statement)

3. For patients with pulmonary sarcoidosis, we suggest that inhaled corticosteroids should not be routinely prescribed to treat the chronic cough. (Grade 2C).

4. For patients with ILD and refractory chronic cough, we suggest trials of therapies recommended for patients with unexplained chronic cough according to the CHEST guidelines, with treatments such as gabapentin and multimodality speech pathology therapy, or entering into clinical trials if available. (Ungraded Consensus-Based Statement)

5. For patients with chronic cough due to ILD, when alternative treatments have failed and the cough is adversely affecting their quality of life, we suggest that opiates be recommended for symptom control in a palliative care setting with reassessment of the benefits and risks at 1 week and then monthly before continuing. (Ungraded Consensus-Based Statement)

CHEST 2018; 154(4):904-917



CHEST 2021; 160(5):1774-1782

TABLE 1] Therapeutic Treatment Trials for Cough in Idiopathic Pulmonary Fibrosis

Study/Year	Study Design	Systematic Evaluation for Causes of Known Chronic Cough	Intervention	Duration	Outcome
Dutta et al[39]/ 2019, n = 45	Pilot, single-center, double-blind, RCT	No	Omeprazole, 20 mg twice daily	3 mo	A nonsignificant 39% reduction in geometric mean cough frequency per hour (95% CI, 0.34 to 1.093)
Kilduff et al[26]/ 2014, n = 18	Cohort	Yes	Omeprazole, 40 mg twice daily or lansoprazole, 30 mg twice daily plus ranitidine, 300 mg at night	8 wk	No significant change in cough frequency ($P = .70$)
van Manen et al[40]/ 2017, n = 43	Multicenter, prospective, observational study	No	Pirfenidone, 2,403 mg/d	12 wk	A clinically significant 34% reduction in 24-h objective cough counts (95% CI, −48% to −15%; $P = .002$)
Horton et al[41]/ 2012, n = 23	Randomized, double-blind, crossover trial	No	Thalidomide, 50-100 mg at night	12 wk	CQLQ scores significantly improved with thalidomide, decreasing by 11.4 points (95% CI, −15.7 to −7.0; $P < .001$)
Birring et al[42]/ 2017, n = 24					ere was a significant 31.1% reduction in mean daytime cough frequency ($P = .0241$)
Hope-Gill et al[33]/ 2003, n = 6					gnificant reduction in visual analog scale score ($P < .05$)

Cromolyn sodium

Inhibition of mast cell degranulation and mast cell-mediated immune activation

Reduction of C-fibre sensory nerve activity

CQLQ = Cough Quality of Life Questionnaire; RCT = randomized controlled trial.

CHEST 2021; 160(5):1774-1782

Treatment

- Low-dose prednisolone
- Neuromodulators
  (gabapentin, pregabalin, amitriptyline, baclofen, opioids)
- Thalidomide
- Antifibrotic agents: pirfenidone, nintedanib (?)
- Speech therapy
- **Azithromycin**
- **Gefapixant ($P2X_3$ receptor antagonist)**
- **Inhaled cromolyn sodium [RVT-1601, formely (PA 101)]**

ORIGINAL RESEARCH

Azithromycin for the Treatment of Chronic Cough in Idiopathic Pulmonary Fibrosis

A Randomized Controlled Crossover Trial

Sabina A. Guler[1], Christian Clarenbach[2], Martin Brutsche[3], Katrin Hostettler[4], Anne-Kathrin Brill[1], Anke Schertel[1], Thomas K. Geiser[1], and Manuela Funke-Chambour[1]

[1]Department of Pulmonary Medicine, Inselspital, Bern University Hospital, University of Bern, Bern, Switzerland; [2]Department of Pulmonary Medicine, University Hospital of Zürich, Zürich, Switzerland; [3]Department of Pulmonary Medicine, Kantonsspital St. Gallen, St. Gallen, Switzerland; and [4]Clinics of Respiratory Medicine, University Hospital of Basel, Basel, Switzerland

Azithromycin: an immunomodulatory and anti-inflammatory antibiotic with antifibrotic properties in vitro and in animal models of lung fibrosis

Two 12-week intervention periods
(azithromycin 500 mg three times per week or placebo three times per week).
25 patient for randomization→ 20 patient completed study

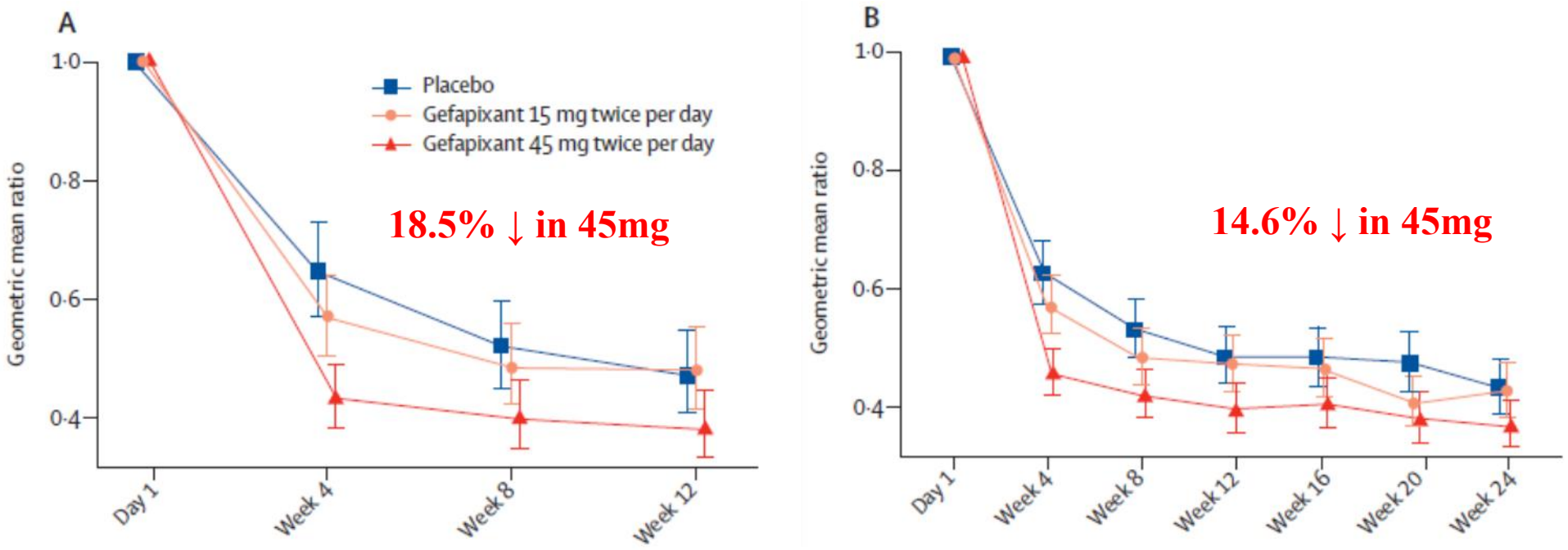
Ann Am Thorac Soc 2021; 18: 2018–2026

	Azithromycin ($n = 20$)			Placebo ($n = 20$)			Between-Period Difference in Change*	
	Before	After	*P* Value	Before	After	*P* Value	Mean Difference (95% CI)	*P* Value
Leicester Cough Questionnaire, score								
Total	11.7 (3.7)	11.3 (3.7)	0.29	11.5 (3.1)	11.7 (3.3)	0.65	0.68 (−0.64 to 1.99)	0.29
Physical	4.3 (1.1)	4.0 (1.0)	0.10	4.3 (0.9)	4.2 (0.9)	0.93	0.28 (−0.23 to 0.73)	0.28
Psychological	3.6 (1.4)	3.5 (1.5)	0.31	3.5 (1.1)	3.6 (1.4)	0.86	0.20 (−0.24 to 0.64)	0.35
Social	3.8 (1.5)	3.8 (1.5)	0.85	3.7 (1.4)	3.9 (1.3)	0.32	0.23 (−0.37 to 0.82)	0.44
Cough VAS, score out of 10	5.6 (2.3)	5.8 (2.1)	0.75	5.8 (2.1)	6.3 (2.1)	0.39	0.25 (−1.12 to 1.63)	0.70
St. George's Respiratory Questionnaire, score								
Total	57.2 (18.6)	59.1 (16.6)	0.32	57.0 (13.8)	60.4 (18.6)	0.18	1.92 (−6.1 to 9.9)	0.62
Activity	69.7 (17.1)	73.1 (18.1)	0.08	70.0 (15.0)	73.8 (17.2)	0.14	0.86 (−6.74 to 8.47)	0.81
Impact	47.6 (21.8)	49.5 (19.5)	0.41	47.4 (14.9)	50.9 (22.5)	0.25	1.88 (−7.30 to 11.1)	0.67
Symptoms	65.3 (22.2)	64.1 (17.8)	0.78	63.7 (17.9)	65.9 (19.3)	0.55	4.59 (−10.9 to 20.0)	0.54

Ann Am Thorac Soc 2021; 18: 2018–2026

Efficacy and safety of gefapixant, a $P2X_3$ receptor antagonist, in refractory chronic cough and unexplained chronic cough (COUGH-1 and COUGH-2): results from two double-blind, randomised, parallel-group, placebo-controlled, phase 3 trials

*Lorcan P McGarvey, Surinder S Birring, Alyn H Morice, Peter V Dicpinigaitis, Ian D Pavord, Jonathan Schelfhout, Allison Martin Nguyen, Qing Li, Anjela Tzontcheva, Beata Iskold, Stuart A Green, Carmen La Rosa, David R Muccino, Jaclyn A Smith, COUGH-1 and COUGH-2 Investigators**

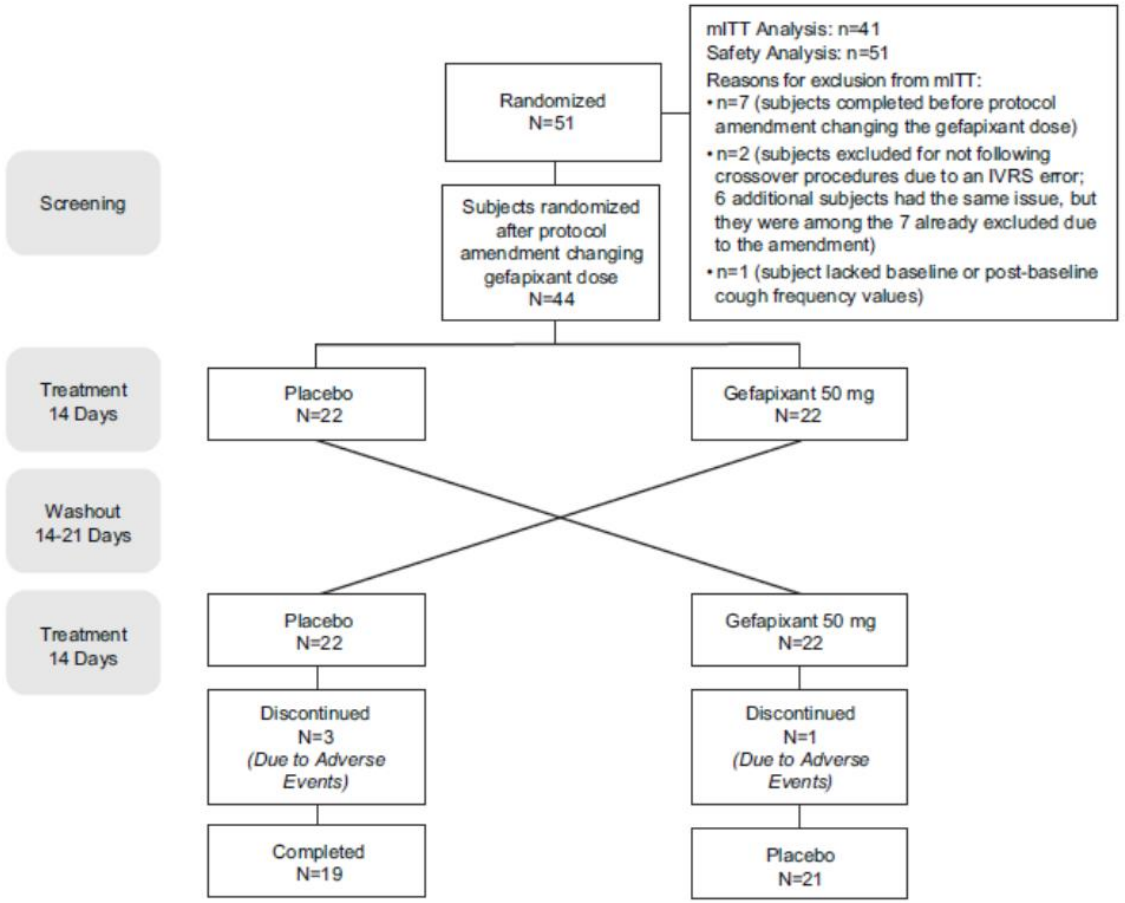


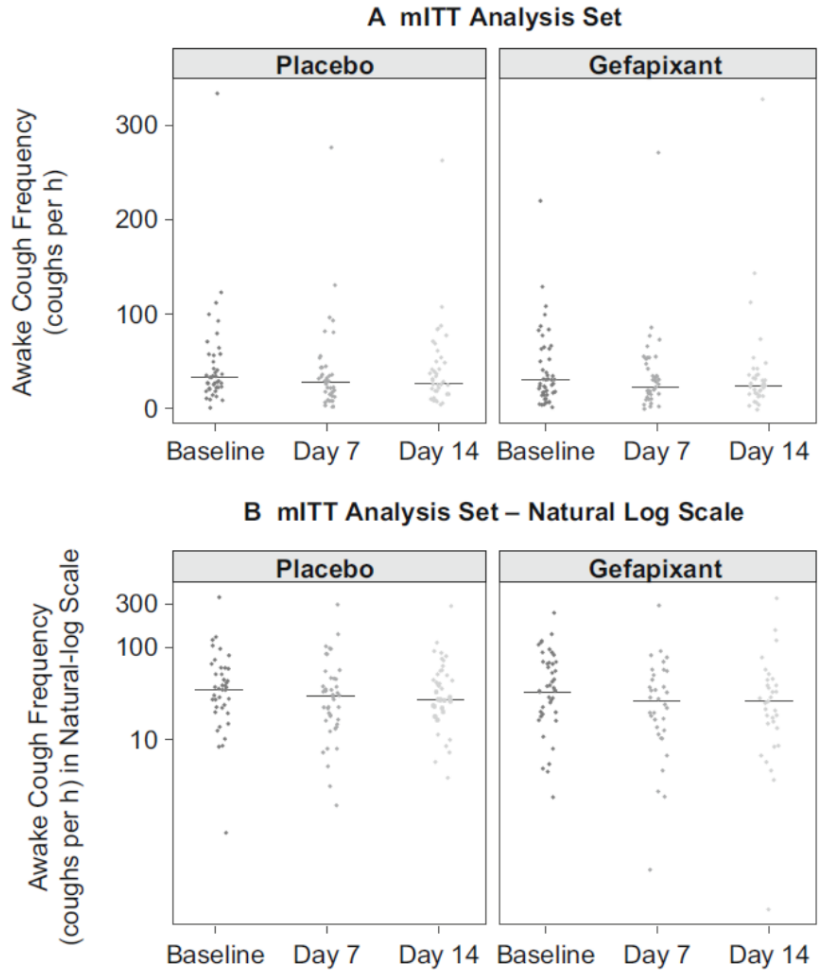
24-h cough frequency over 12 weeks in COUGH-1 (A) and 24 weeks in COUGH-2 (B)

Lancet 2022; 399: 909–23

Treatment of Persistent Cough in Subjects with Idiopathic Pulmonary Fibrosis (IPF) with Gefapixant, a P2X3 Antagonist, in a Randomized, Placebo-Controlled Clinical Trial

Fernando J. Martinez · Amna Sadaf Afzal · Jaclyn A. Smith · Anthony P. Ford · Jerry Jing Li · Yuping Li · Michael M. Kitt on behalf of the Chronic Cough in IPF Study Group





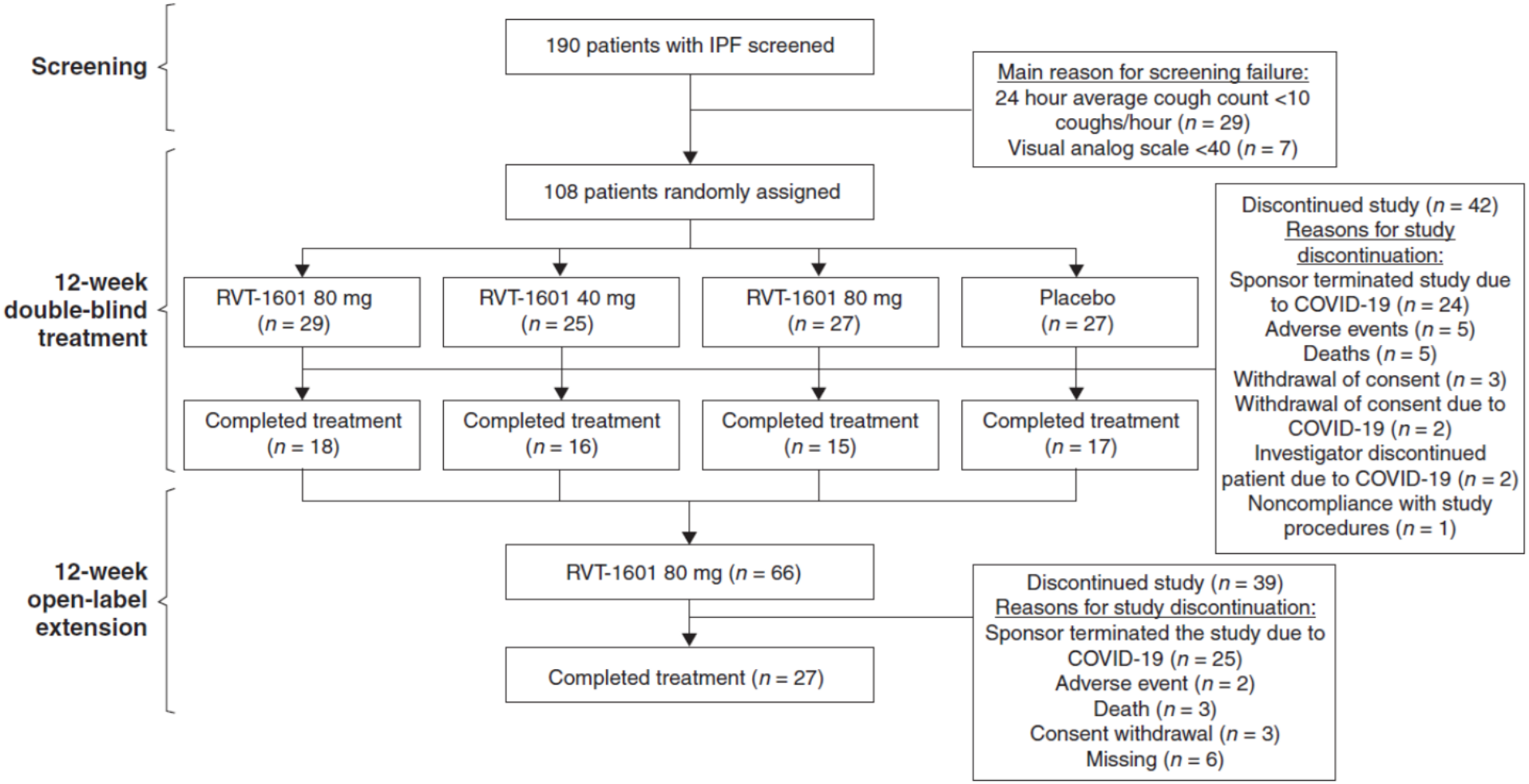
Pulm Ther 2021; 7:471–486

Phase 2B Study of Inhaled RVT-1601 for Chronic Cough in Idiopathic Pulmonary Fibrosis

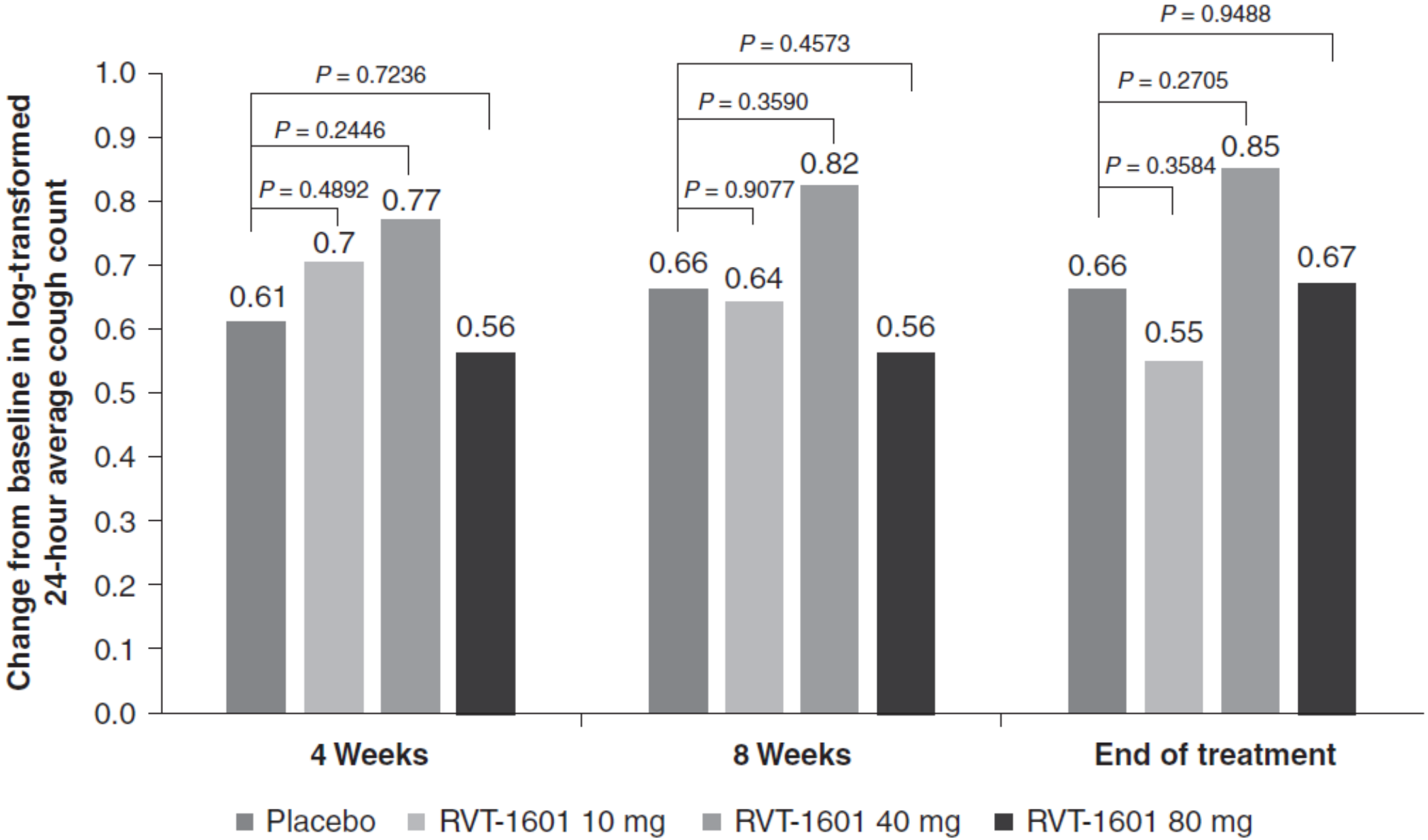
A Multicenter, Randomized, Placebo-controlled Study (SCENIC Trial)

Cromolyn sodium

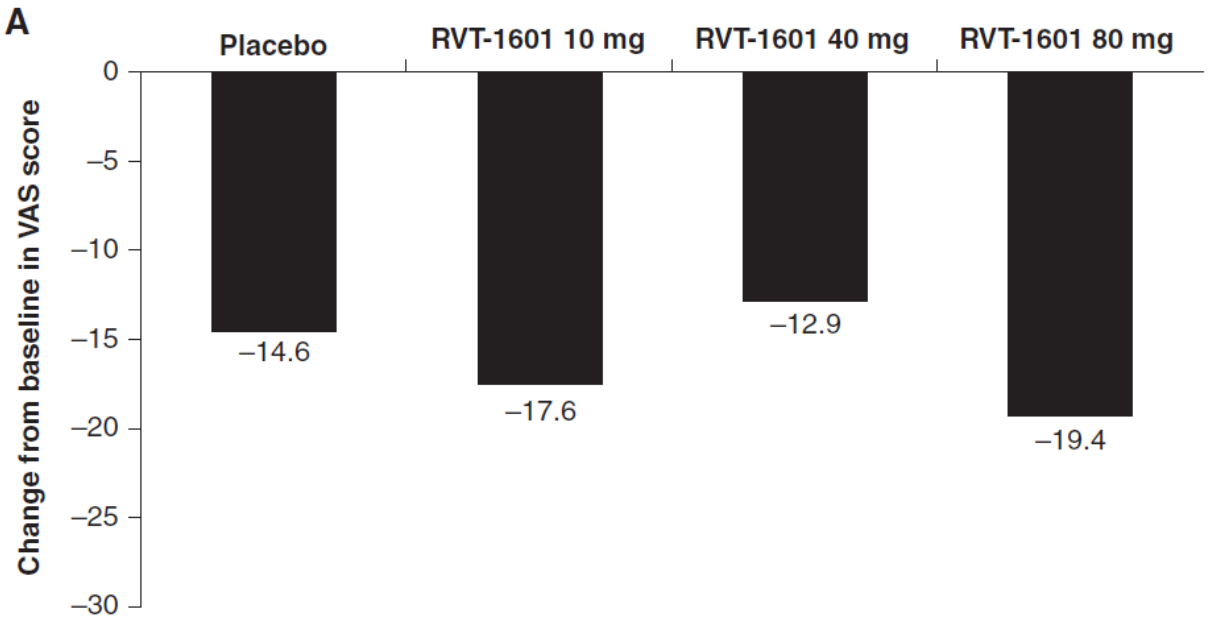
Fernando J. Martinez[1], Marlies S. Wijsenbeek[2], Ganesh Raghu[3,4], Kevin R. Flaherty[5], Toby M. Maher[6,7,8], Wim A. Wuyts[9], Michael Kreuter[10,11], Martin Kolb[12], Daniel C. Chambers[13,14], Charles Fogarty[15], Nesrin Mogulkoc[16], Ahmet S. Tutuncu[17], and Luca Richeldi[18]

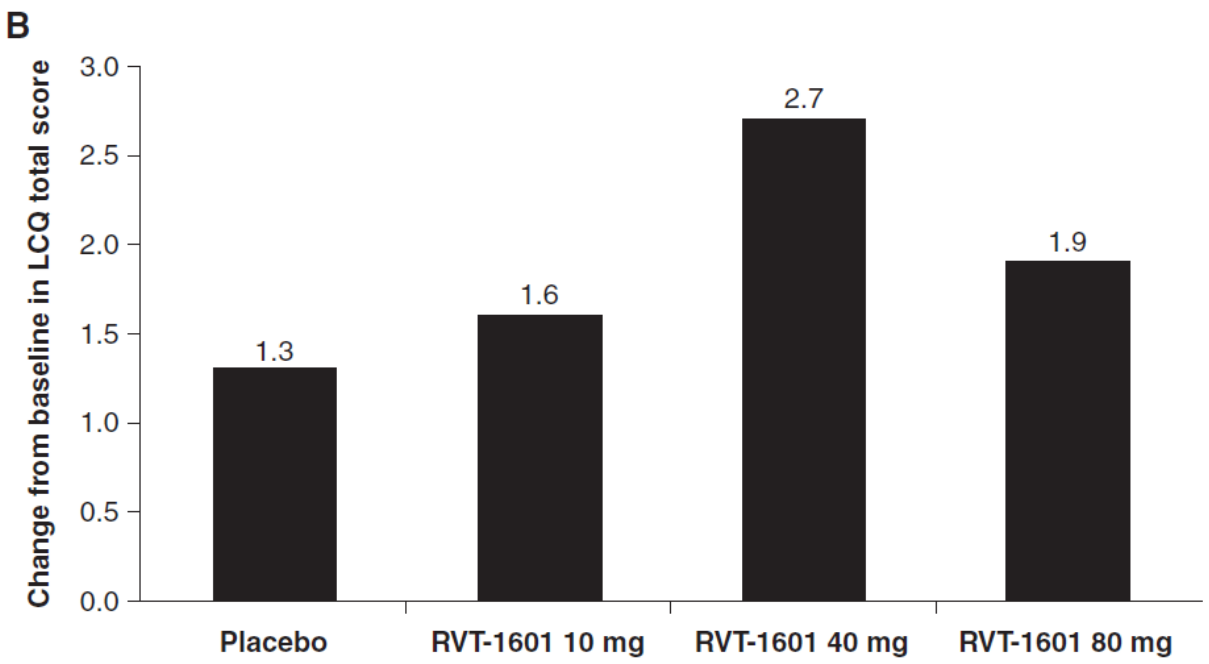


Am J Respir Crit Care Med 2022; 205:1084–1092



Am J Respir Crit Care Med 2022;205:1084–1092



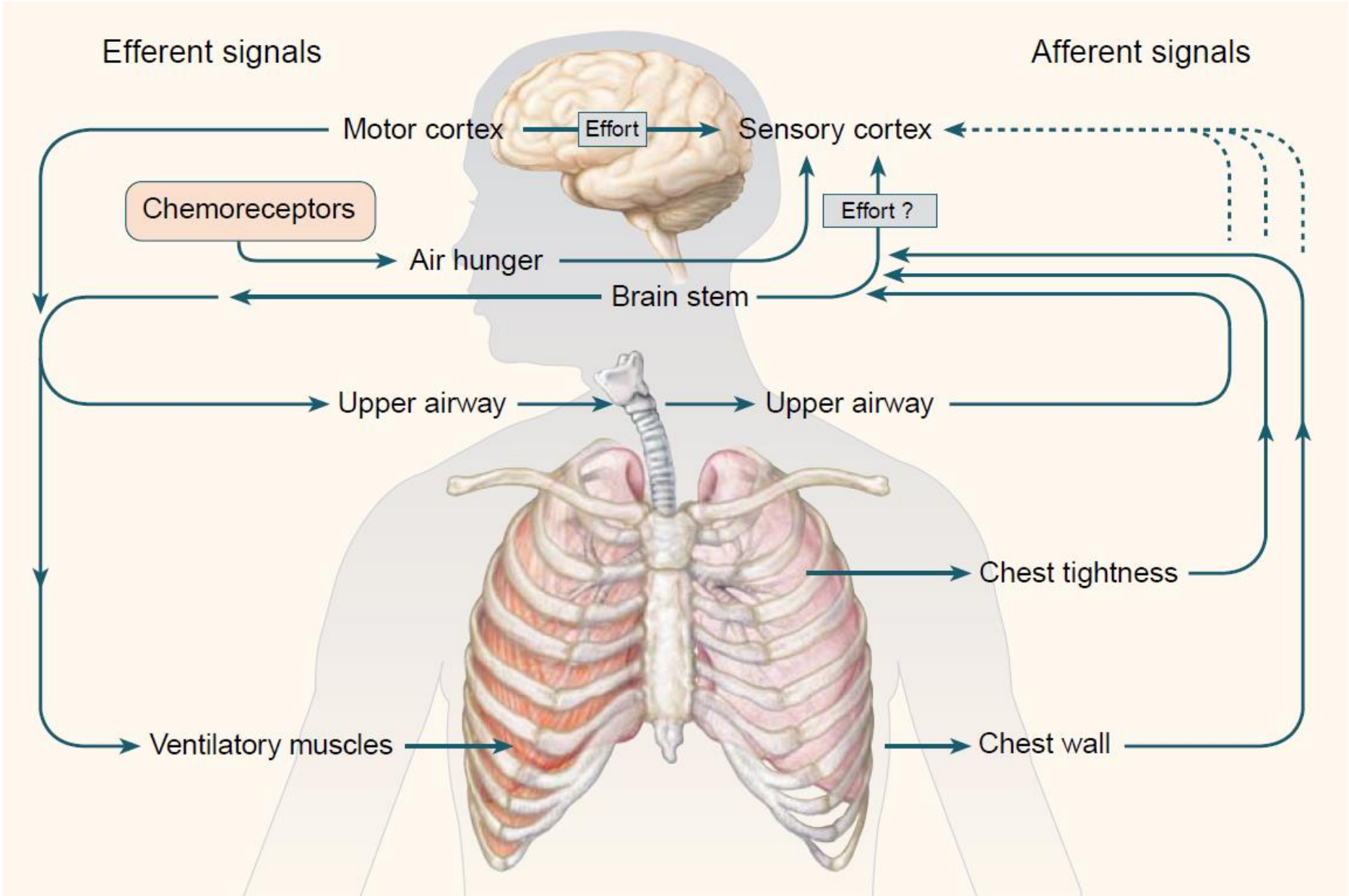


Am J Respir Crit Care Med 2022;205:1084–1092

Dyspnea

- dys (‘painful’, ‘difficult’) and pneuma (‘breath’)
- Subjective experience of breathing discomfort that consists of qualitatively distinct sensations that vary in intensity

  (1999 ATS consensus statement)
- Common in ILD (up to 90% in IPF)
- Severity → quality of life and mortality in patients with ILD

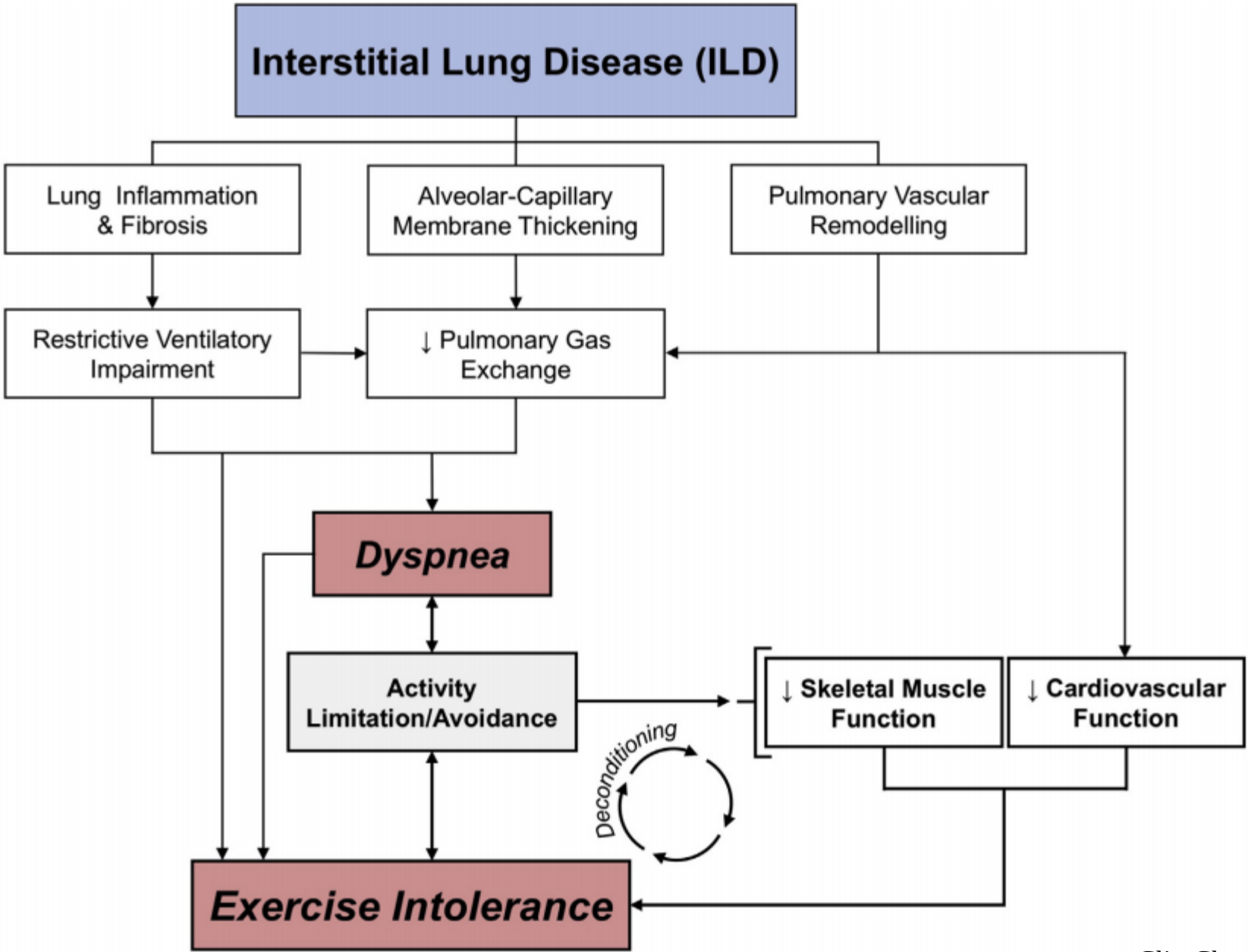


N Engl J Med 1995; 333:1547-1553

TABLE 2. POSSIBLE AFFERENT SOURCES FOR RESPIRATORY SENSATION*

Source of Sensation	Adequate Stimulus
Medullary respiratory corollary discharge	Drives to automatic breathing (hypercapnia, hypoxia, exercise)
Primary motor cortex corollary discharge	Voluntary respiratory drive
Limbic motor corollary discharge	Emotions
Carotid and aortic bodies	Hypercapnia, hypoxemia, acidosis
Medullary chemoreceptors	Hypercapnia
Slowly adapting pulmonary stretch receptors	Lung inflation
Rapidly adapting pulmonary stretch receptors	Airway collapse, irritant substances, large fast (sudden) lung inflations/deflations
Pulmonary C-fibers (J-receptors)	Pulmonary vascular congestion
Airway C-fibers	Irritant substances
Upper airway "flow" receptors	Cooling of airway mucosa
Muscle spindles in respiratory pump muscles	Muscle length change with breathing motion
Tendon organs in respiratory pump muscles	Muscle active force with breathing motion
Metaboreceptors in respiratory pump muscles	Metabolic activity of respiratory pump
Vascular receptors (heart and lung)	Distention of vascular structures
Trigeminal skin receptors	Facial skin cooling
Chest wall joint and skin receptors	Tidal breathing motion

Am J Respir Crit Care Med 2012; 185: 435–452



Clin Chest Med 2019; 40: 405–420

Dyspnea and comorbidities

- **COPD**
- **Pulmonary hypertension**
- **Obesity**
- **Obstructive sleep apnea**
- **Depression**

Management

- **Disease-modifying pharmacotherapy (antifibrotic drugs)**
- **Control of comorbidities**
  (bronchodilators, sildenafil or inhaled treprostinil)
- **Benzodiazepine, opioids or antidepressant (depression)**
- **Pulmonary rehabilitation**
- **Oxygen therapy**

Oxygen therapy

- **Decrease or prevent short of breath**
- **Decrease risk of pulmonary hypertension**
- **Lower heart rate**
- **Increase activity level**
- **Improve sleep quality**

AMERICAN THORACIC SOCIETY DOCUMENTS

Home Oxygen Therapy for Adults with Chronic Lung Disease

An Official American Thoracic Society Clinical Practice Guideline

Susan S. Jacobs, Jerry A. Krishnan, David J. Lederer, Marya Ghazipura, Tanzib Hossain, Ai-Yui M. Tan, Brian Carlin, M. Bradley Drummond, Magnus Ekström, Chris Garvey, Bridget A. Graney, Beverly Jackson, Thomas Kallstrom, Shandra L. Knight, Kathleen Lindell, Valentin Prieto-Centurion, Elisabetta A. Renzoni, Christopher J. Ryerson, Ann Schneidman, Jeffrey Swigris, Dona Upson, and Anne E. Holland; on behalf of the American Thoracic Society Assembly on Nursing

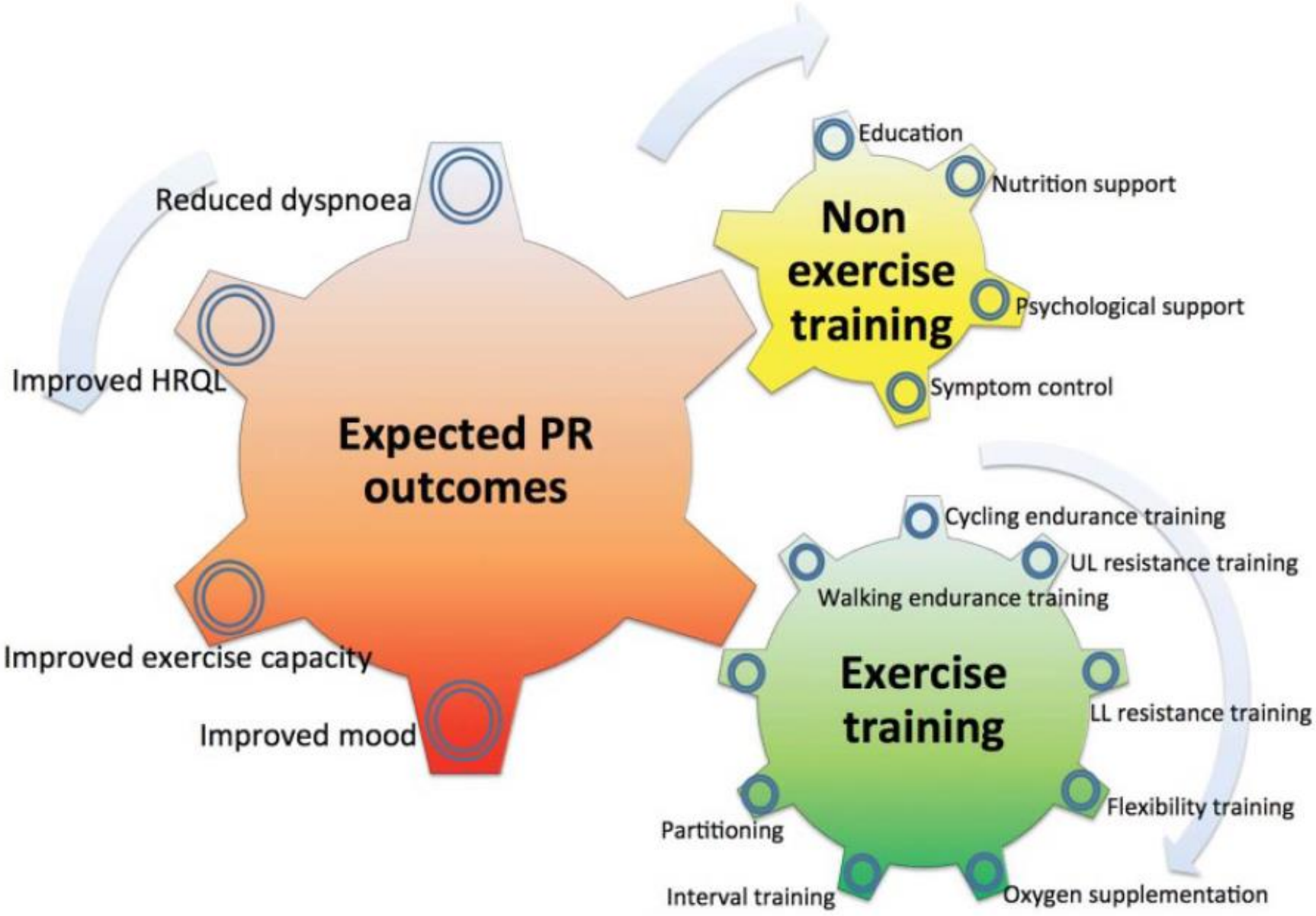
- **For adults with interstitial lung disease (ILD) who have severe chronic resting room air hypoxemia, we recommend prescribing long-term oxygen therapy for at least 15 h/d (strong recommendation, very-low-quality evidence).**
- **For adults with ILD who have severe exertional room air hypoxemia, we suggest prescribing ambulatory oxygen (conditional recommendation, low-quality evidence).**

Am J Respir Crit Care Med 2020; 202: pp e121–e141

Term	Definition
Ambulatory oxygen	Oxygen delivered during exercise or activities of daily living.
Continuous-flow oxygen	Oxygen delivered at a constant flow rate, regardless of the respiratory rate, in contrast to pulse-dose oxygen (*see below*).
Continuous oxygen	Oxygen prescribed 24 h/d.
Home oxygen	Oxygen delivered in a home, also known as domiciliary oxygen. It includes not only long-term oxygen but also short-term, nocturnal, palliative, ambulatory, and short-burst oxygen. It excludes oxygen use in healthcare and emergency settings.
Long-term oxygen	Oxygen that is delivered to patients with chronic hypoxemia, in most cases for the remainder of the patient's life. Long-term oxygen therapy is prescribed for at least 15 h/d.
Nocturnal oxygen	Oxygen delivered during sleep time only.
Palliative oxygen	Oxygen to relieve dyspnea. Palliative oxygen may be provided continuously, nocturnally, or during ambulation. Short-burst oxygen therapy falls into this category.
Portable oxygen	Oxygen delivered through systems that are sufficiently lightweight so that they can be carried or pulled by patients and allow them to leave their home (e.g., oxygen cylinders or canisters carried or pulled in trolleys or portable oxygen concentrators).
Pulse-dose oxygen	Oxygen delivered during inspiration only in such a way that the quantity of oxygen administered is influenced by the respiratory rate. The delivery system is at rest while the patient is exhaling.
Short-burst oxygen	Brief and intermittent oxygen administration before and/or after exercise, generally used as needed, in the absence of known hypoxemia.
Short-term oxygen therapy	Oxygen provided temporarily, during a period of severe hypoxemia (e.g., during the course of and shortly after an exacerbation of COPD).

Am J Respir Crit Care Med 2020; 202: pp 1345–1359

Pulmonary rehabilitation



Ther Adv Respir Dis 2017; 11 115–128

Cochrane Library

Cochrane Database of Systematic Reviews

Pulmonary rehabilitation for interstitial lung disease (Review)

Dowman L, Hill CJ, May A, Holland AE

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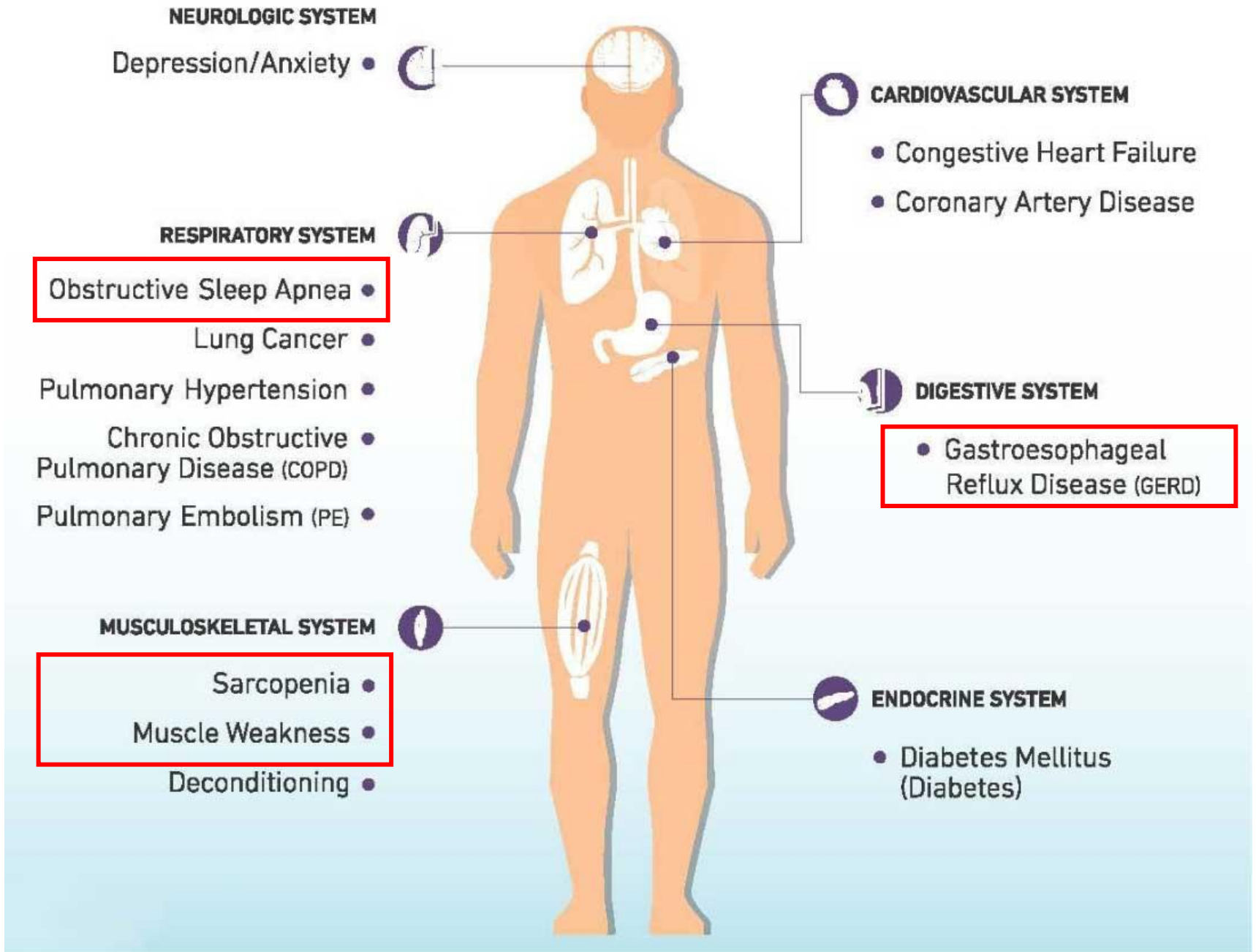
DOI: 10.1002/14651858.CD006322.pub4.

Pulmonary rehabilitation compared to no pulmonary rehabilitation for interstitial lung disease

Patient or population: interstitial lung disease
Setting: pulmonary rehabilitation centres
Intervention: pulmonary rehabilitation
Comparison: no pulmonary rehabilitation

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with no pulmonary rehabilitation	Risk with pulmonary rehabilitation				
Change in 6MWD assessed with: 6MWT Follow-up: range 3–48 weeks	The mean change in 6MWD ranged from –35 metres to 26 metres	**MD 40.07 metres higher** (32.70 higher to 47.44 higher)	—	585 (13 RCTs)	⨁⨁⨁◯ **Moderate**[a]	Sensitivity analysis from studies at lower risk of bias was similar (MD 41.22 metres, 95% CI 26.80 to 55.64; 5 RCTs, 288 participants; I^2 = 35%).
Change in 6MWD at long-term follow-up assessed with: 6MWT Follow-up: range 6–11 months	The mean change in 6MWD at long-term follow-up ranged from –49 metres to –6 metres	**MD 32.43 metres higher** (15.58 higher to 49.28 higher)	—	321 (6 RCTs)	⨁⨁⨁◯ **Moderate** [b]	—
Change in peak work capacity assessed with: cardiopulmonary exercise test Follow-up: range 8 weeks to 6 months	The mean change in peak work capacity ranged from –10 watts to 0.6 watts	**MD 9.04 watts higher** (6.07 higher to 12.0 higher)	—	159 (4 RCTs)	⨁⨁◯◯ **Low** [c,d]	—
Change in dyspnoea score Follow-up: range 8 weeks to 6 months	The mean change in dyspnoea score ranged from –0.2 to 0.4	**SMD 0.36 SD lower** (0.58 lower to 0.14 lower)	—	348 (7 RCTs)	⨁⨁◯◯ **Low** [e,f]	Lower value post intervention is favourable, indicating improvement in dyspnoea. Sensitivity analysis from studies at lower risk of bias was similar (SMD –0.28, 95% CI –0.51 to –0.04; 5 RCTs, 288 participants; I^2 = 70%). SMD of –0.36 corresponds to MD of –0.32 points when re-expressed on the

						modified Medical Research Dyspnoea Scale (0–4, 5-point score, 0 indicates no dyspnoea).
Change in quality of life assessed with: SGRQ Total score Follow-up: range 8–48 weeks	The mean change in quality of life ranged from –7 to 6 points	**MD 9.29 points lower** (11.06 lower to 7.52 lower)	—	478 (11 RCTs)	⨁⨁⨁◯ **Moderate** [a]	Lower value post intervention is favourable, indicating improvement in quality of life. Sensitivity analysis from studies at lower risk of bias was similar (MD –8.13, 95% CI –11.24 to –5.02; 4 RCTs, 231 participants; I^2 = 21%).
Change in quality of life at long-term assessed with: SGRQ Total score Follow-up: 6–11 months	The mean change in quality of life at long-term follow-up ranged from –1 to 5 points	**MD 4.93 points lower** (7.81 lower to 2.06 lower)	—	240 (4 RCTs)	⨁⨁◯◯ **Low** [c,f]	Lower value post intervention is favourable, indicating improvement in quality of life.
Long-term survival (incidence of mortality) Follow-up: range 6–11 months	**Study population**		**OR 0.40** (0.14 to 1.12)	291 (4 RCTs)	⨁⨁◯◯ **Low** [c,g]	Lower OR represents improved survival at long-term follow-up.
	85 per 1000	36 per 1000 (13 to 94)				



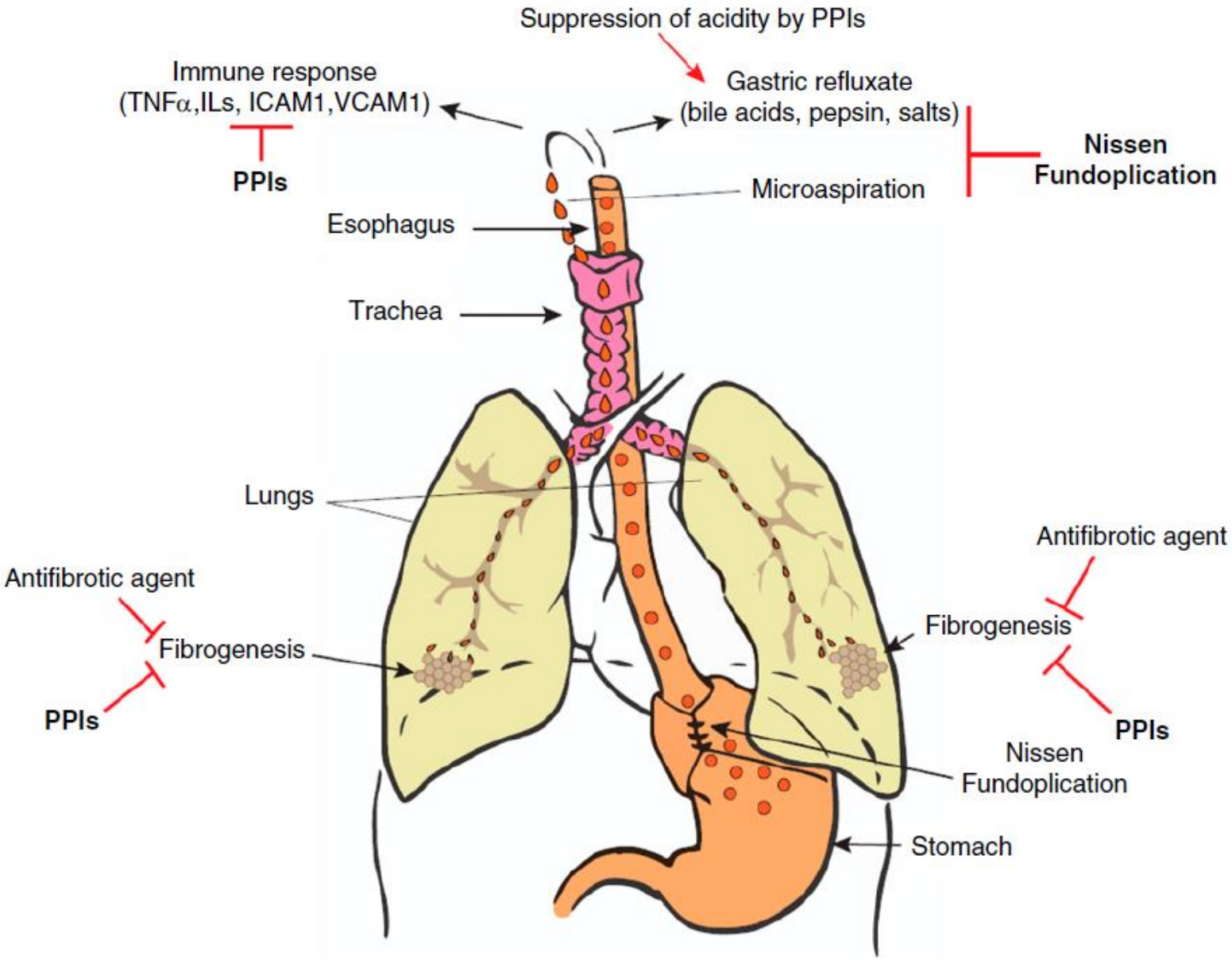
Pulmonary Fibrosis Foundation

Gastroesophageal Reflux Disease

- **The prevalence: ～ 90%**
- **Risk factor for aspiration and microaspiration**
- **Possible mechanism for development and progression of IPF**
- **2011 and 2015 updated guideline for IPF**

  Regular antacid treatment for patients with IPF

  (conditional recommendation, very low confidence in estimates of effect)



Microaspiration: gastric juice/contents (acid/alkaline; pepsin, bile)

↓

Aberrant wound healing

↓

Pulmonary fibrosis

Am J Respir Crit Care Med 2016;193:1345–1352

Antacid therapy and disease outcomes in idiopathic pulmonary fibrosis: a pooled analysis

Michael Kreuter, Wim Wuyts, Elisabetta Renzoni, Dirk Koschel, Toby M Maher, Martin Kolb, Derek Weycker, Paolo Spagnolo, Klaus-Uwe Kirchgaessler, Felix J F Herth, Ulrich Costabel

Summary

Background Gastro-oesophageal reflux disease is a potential risk factor for the development and progression of idiopathic pulmonary fibrosis (IPF). We aimed to investigate the effect of antacid therapy on disease progression in patients randomly assigned to placebo through analysis of three large, phase 3 trials of pirfenidone in IPF.

Methods Patients with IPF from the placebo groups of three trials of pirfenidone (CAPACITY 004, CAPACITY 006, and ASCEND) were included in this post-hoc analysis. We analysed effects of antacid therapy use from baseline for pulmonary function, exercise tolerance, survival, hospital admission, and adverse events for 52 weeks with and without adjustment for potential confounders. The primary endpoint, disease progression by 1 year, was defined as a decrease in predicted forced vital capacity (FVC) by 10% or more, a decrease in 6 min walk distance (6MWD) by 50 m or more, or death. We did survival analyses with the Kaplan-Meier estimator and evaluated using the log-rank test.

Findings Of 624 patients, 291 (47%) received antacid therapy and 333 (53%) did not. At 52 weeks, we noted no significant difference between groups for disease progression (114 [39%] for antacid therapy *vs* 141 [42%] for no antacid therapy, p=0·4844). Rates also did not differ for all-cause mortality (20 [7%] *vs* 22 [7%], p=0·8947), IPF-related mortality (11 [4%] *vs* 17 [5%]; p=0·4251), absolute FVC decrease by 10% or more (49 [17%] *vs* 64 [19%]; p=0·4411), or mean observed change in FVC (% predicted –4·9% [SD 6·4] *vs* –5·5% [7·2], p=0·3355; observed volume –0·2 L [0·3] *vs* –0·2 L [0·3], p=0·4238). The rate of hospital admission was non-significantly higher in the antacid therapy group (65 [22%] *vs* 54 [16%]; p=0·0522). When stratified by baseline FVC (<70% or ≥70%), disease progression, mortality, FVC, 6MWD, and hospital admission did not differ between groups. Adverse events were similar between treatment and no treatment groups; however, overall infections (107 [74%] *vs* 101 [62%]; p=0·0174) and pulmonary infections (20 [14%] *vs* 10 [6%]; p=0·0214) were higher in patients with advanced IPF (ie, FVC <70%) who were treated with antacids than not treated with antacids.

Interpretation Antacid therapy did not improve outcomes in patients with IPF and might potentially be associated with an increased risk of infection in those with advanced disease.

Lancet Respir Med 2016; 4: 381-89

Antacid Medication and Antireflux Surgery in Patients with Idiopathic Pulmonary Fibrosis

A Systematic Review and Meta-Analysis

Yet H. Khor[1,2], Brittany Bissell[3,4], Marya Ghazipura[5,6], Derrick Herman[7], Stephanie M. Hon[8], Tanzib Hossain[9], Fayez Kheir[10], Shandra L. Knight[11], Michael Kreuter[12], Madalina Macrea[13], Manoj J. Mammen[14], Maria Molina-Molina[15], Moises Selman[16], Marlies Wijsenbeek[17], Ganesh Raghu[18], and Kevin C. Wilson[19]

Results: For antacid medication, when two studies were aggregated, there was no statistically significant effect on disease progression, defined as a 10% or more decline in FVC, more than 50-m decline in 6-minute walking distance, or death (risk ratio [RR], 0.88; 95% confidence interval [CI], 0.76–1.03). A separate study that could not be included in the meta-analysis found no statistically significant effect on disease progression when defined as a 5% or more decline in FVC or death (RR, 1.10; 95% CI, 1.00–1.21) and an increase in disease progression when defined as a 10% or more decline in FVC or death (RR, 1.28; 95% CI, 1.08–1.51). For antireflux surgery, there was also no statistically significant effect on disease progression (RR, 0.29; 95% CI, 0.06–1.26). Neither antacid medications nor antireflux surgery was associated with improvements in the other outcomes.

Conclusions: There is insufficient evidence to conclude that antacid medication or antireflux surgery improves respiratory outcomes in patients with IPF, most of whom had not had abnormal GER confirmed. Well-designed and adequately powered prospective studies with objective evaluation for GER are critical to elucidate the role of antacid medication and antireflux surgery for respiratory outcomes in patients with IPF.

Ann Am Thorac Soc 2022; 19: pp 833–844

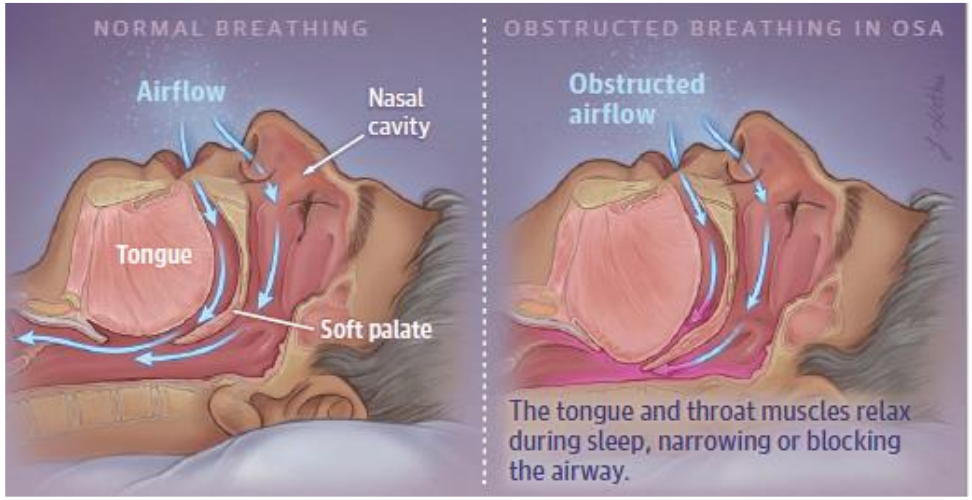
Evidence-based Recommendations for Treatment of IPF

We suggest not treating patients with IPF with antacid medication for the purpose of improving respiratory outcomes (conditional recommendation, very low quality evidence). *Remarks: Antacid medication and other interventions may be appropriate for patients with both IPF and symptoms of gastroesophageal reflux disease (GERD) for the purpose of improving gastroesophageal reflux (GER)–related outcomes in accordance with GER-specific guidelines.*

We suggest not referring patients with IPF for antireflux surgery for the purpose of improving respiratory outcomes (conditional recommendation, very low quality evidence). *Remarks: Antireflux surgery may be appropriate for patients with both IPF and symptoms of GERD for the purpose of improving GER-related outcomes in accordance with GER-specific guidelines.*

Am J Respir Crit Care Med 2022; 205: pp e18–e47

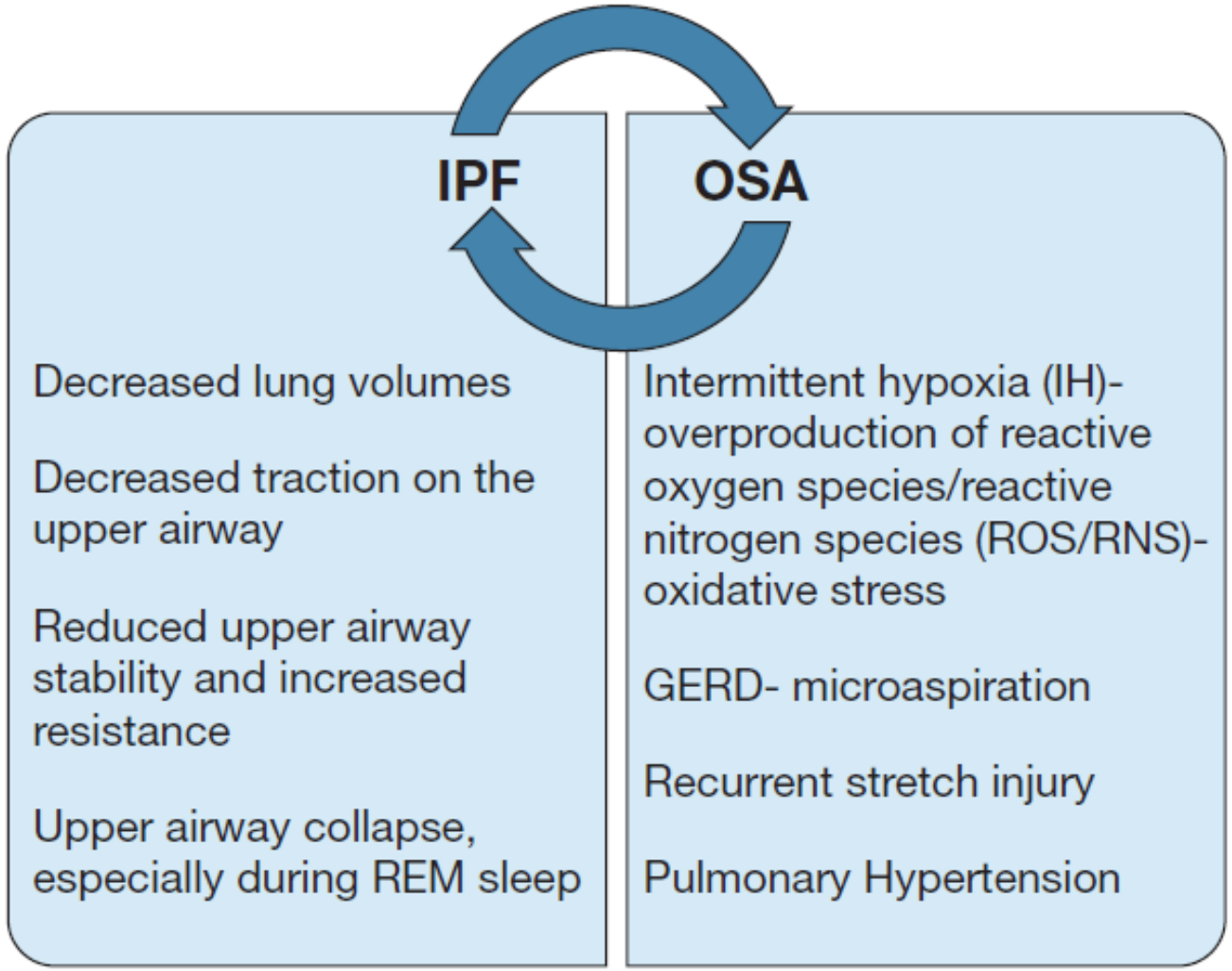
Obstructive sleep apnea



- Prevalence: 59-62%
- Daytime fatigue (43-75%), sleep onset and maintenance insomnia (52-67%), nocturnal cough (48-56%)
- Decreased sleep efficiency, decreased REM sleep stage and increased stage 1, more arousals and sleep fragmentation
- Poor quality of life, increased cough, severity of ILD and mortality

Sleep Breath 2010; 14:387–390
Eur Respir J 2017; 49: 1601934

Possible pathophysiologic pathways connecting IPF and OSA



CHEST 2017; 152(6):1327-1338

RESEARCH ARTICLE

Obstructive sleep apnea in patients with interstitial lung disease: Prevalence and predictive factors

Jae Ha Lee[1], Chan Sun Park[2], Jin Woo Song[3]*

Prevalence of OSA, 53.5% (46/86)

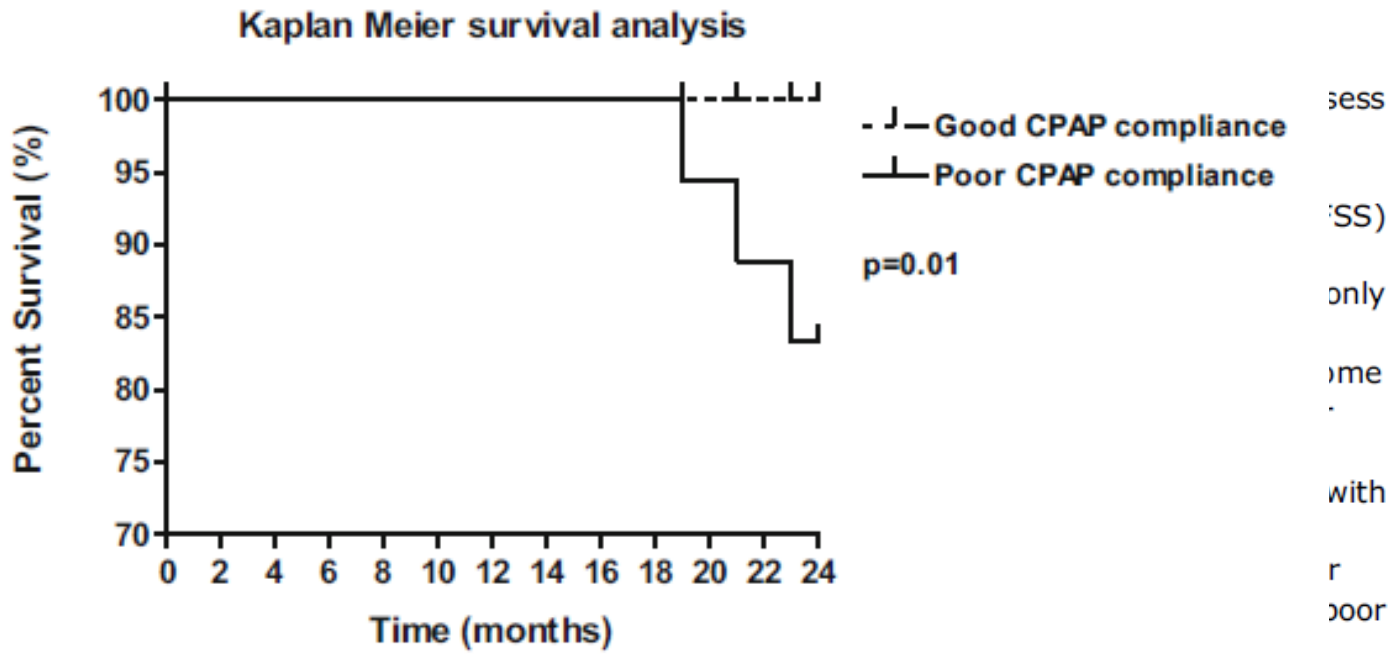
ILD	OSA (n=46)	No OSA (n=40)
IPF	37 (80.4)	37 (80)
NSIP	2 (4.3)	3 (7.5)
CTD	4 (8.7)	10 (25)
COP	0 (0)	5 (12.5)
HP	3 (6.5)	1 (2.5)

Independent factor predicting OSA
Older age, higher body weight and DM

PLoS ONE 15(10): e0239963

TABLE 3] Studies Related to Sleep in Patients With IPF: Subsequent CPAP Treatment Studies (After the 2002 Criteria for IPF)

Study/Year	Methods	Patient Description	Control Group	Key Features and Results
Mermigkis et al[17]/ 2010	Type 1 PSG	CPAP therapy was started in 12 patients with IPF with moderate to severe OSA	None	A statistically significant improvement was observed in the FOSQ 1, 3, and 6 months after CPAP initiation. Improvement, although not statistically significant, was noted in the ESS score, PSQI, FSS, and BDI. The probability of poor CPAP compliance was high and could be eliminated only with intense follow-up by the CPAP clinic staff.
Mermigkis et al[75]/ 2015	Type 1 PSG			



Sarcopenia (근감소증)

- Progressive and generalized skeletal muscle disorder that involves the accelerated loss of muscle mass and function
- Increased adverse outcome (e.g. falls, functional decline, frailty and mortality)
- Prevalence : 32.1 % (males: 31.4%; females: 33.3%) in ILD

Nutritional

- Low protein intake
- Low energy intake
- Micronutrient deficiency
- Malabsorption and other gastrointestinal conditions
- Anorexia (ageing, oral problems)

Associated with inactivity

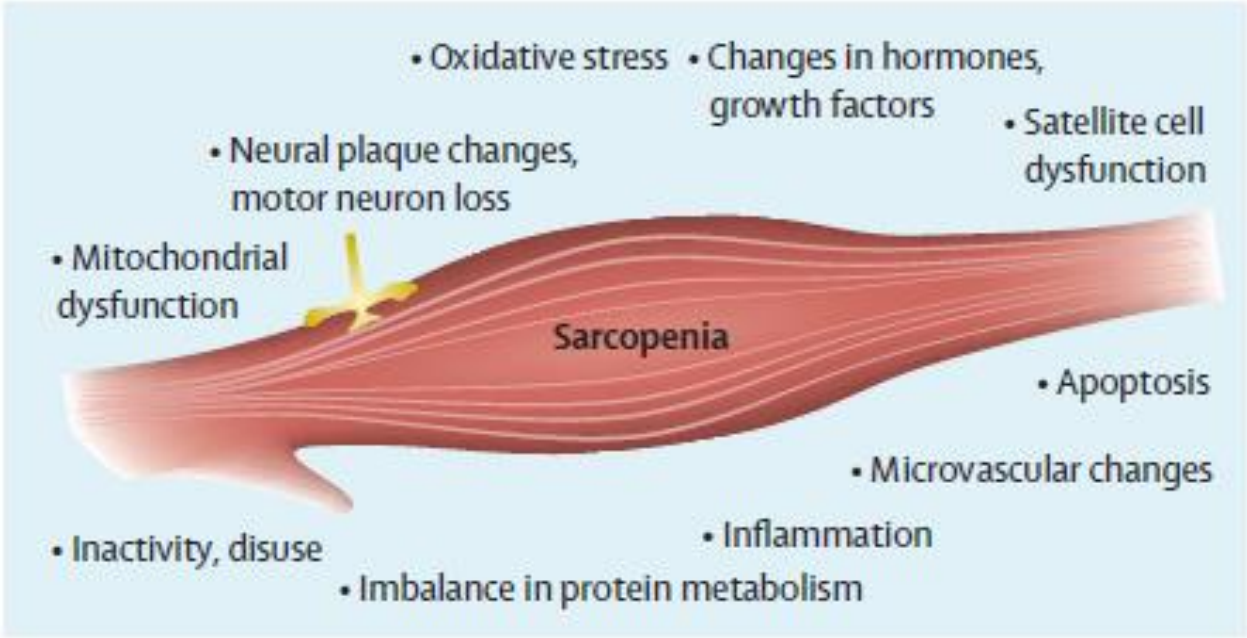
- Bed rest, immobility, deconditioning
- Low activity, sedentary lifestyle

Disease

- Bone and joint diseases
- Cardiorespiratory disorders including chronic heart failure and chronic obstructive pulmonary disease
- Metabolic disorders (particularly diabetes)
- Endocrine diseases (particularly androgen deprivation)
- Neurological disorders
- Cancer
- Liver and kidney disorders

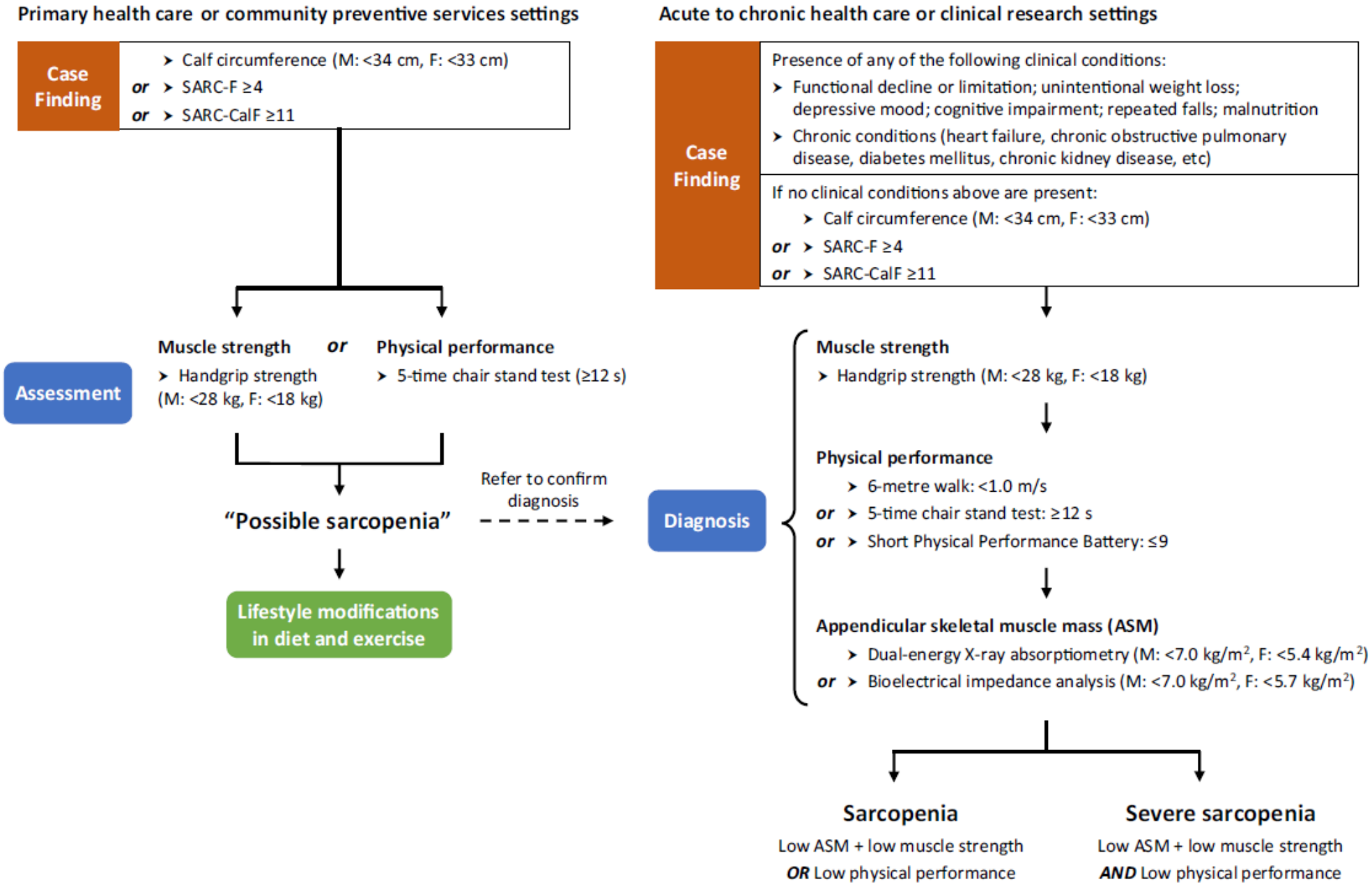
Iatrogenic

- Hospital admission
- Drug-related



Lancet 2019; 393: 2636-46

2019 Asian Working Group for Sarcopenia



Moon *et al. Respiratory Research* (2019) 20:35
https://doi.org/10.1186/s12931-019-1001-6

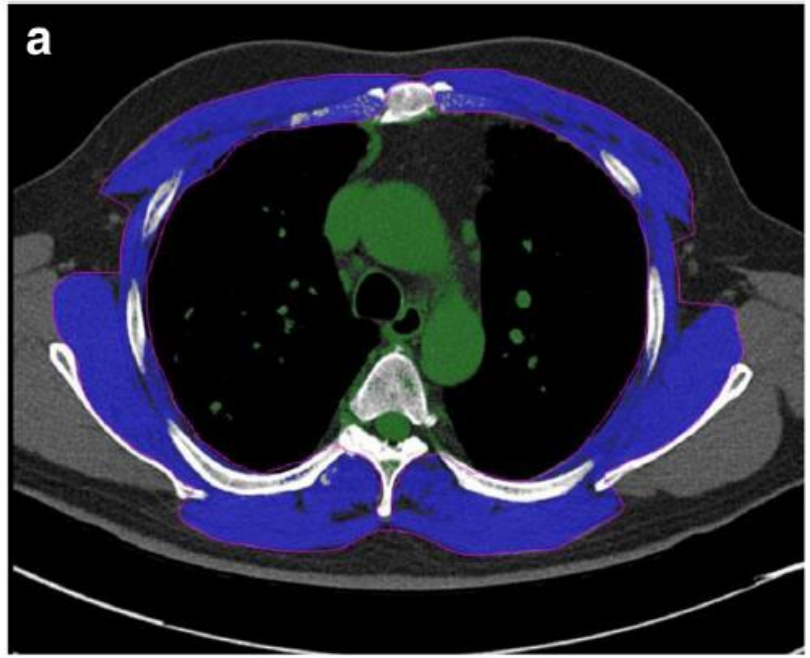
Respiratory Research

RESEARCH Open Access

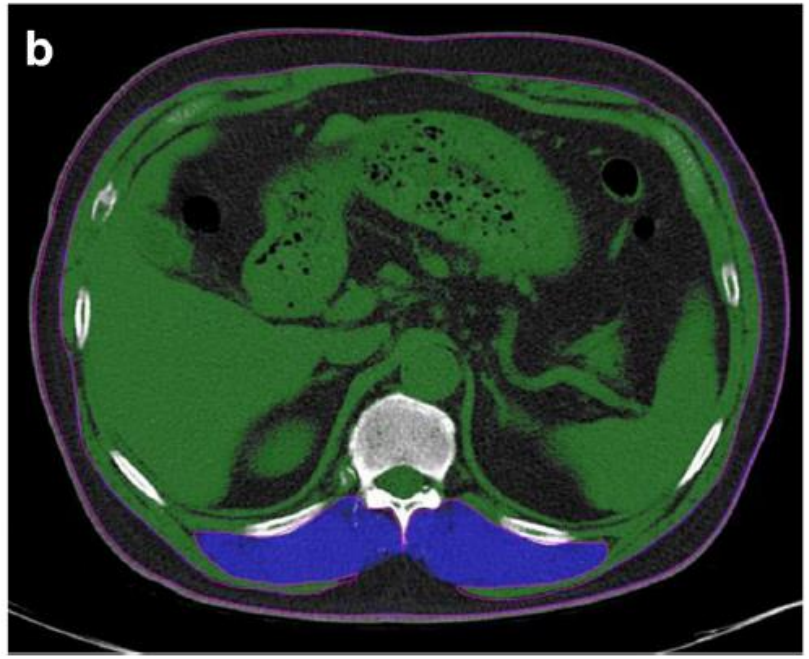
Thoracic skeletal muscle quantification: low muscle mass is related with worse prognosis in idiopathic pulmonary fibrosis patients

Sung Woo Moon, Ji Soo Choi, Sang Hoon Lee, Kyung Soo Jung, Ji Ye Jung, Young Ae Kang, Moo Suk Park, Young Sam Kim, Joon Chang and Song Yee Kim*

- ✓ **180 IPF patients**
- ✓ **Thoracic muscle (e.g. pectoralis, intercostalis, paraspinals, serratus, latissimus muscles) CSA, measured at the T4 level**
- ✓ **Erector spinae muscle (ESM) CSA at the T12 level**



Thoracic muscle (e.g. pectoralis, intercostalis, paraspinals, serratus, latissimus muscles) CSA at T4 level measured at T4 (T4 CSA) CSA of skeletal muscle (cm2) at the T4 level divided by by height squared (m2): T4MI



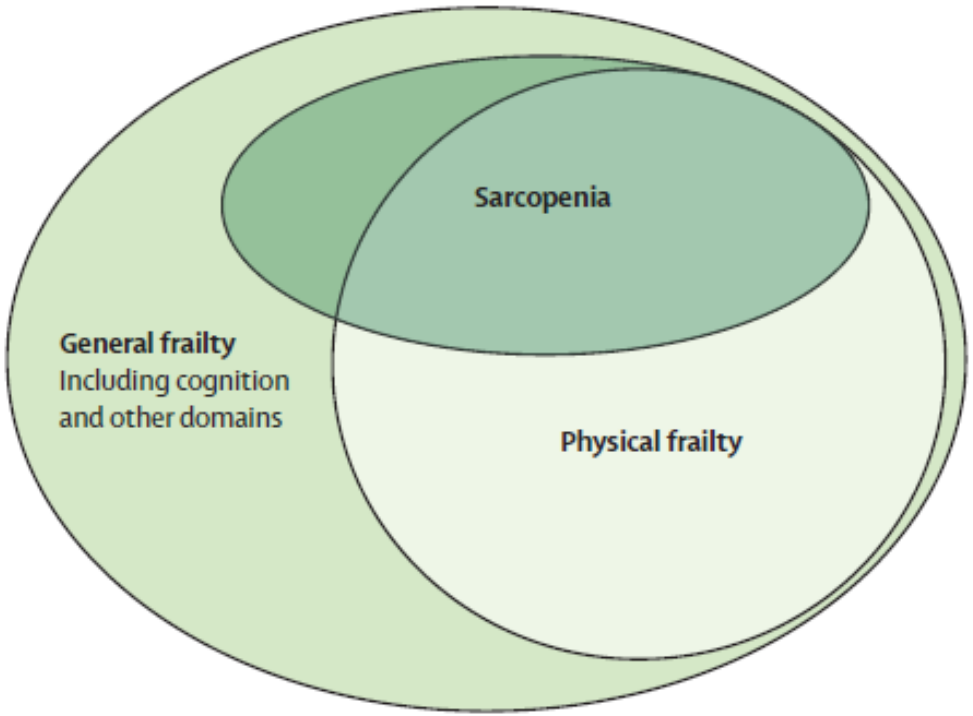
Erector spinae muscle (ESM) at T12 level the CSA of ESM (ESMCSA, cm2) at the T12 level divided by height squared (m2): T12MI

Clinical factors associated with all-cause mortality in the entire cohort (multivariate analysis)

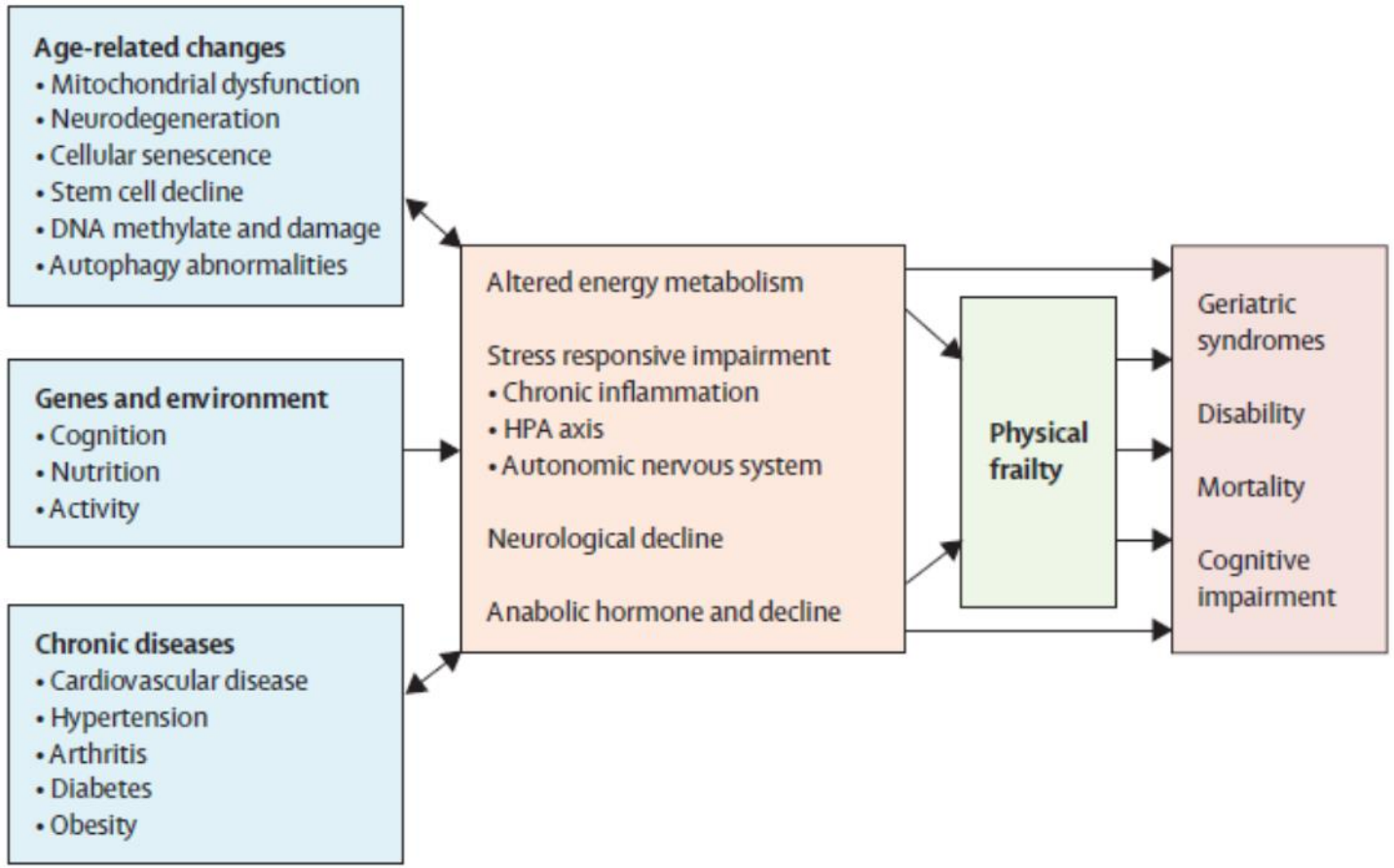
Variables	HR	95% CI	P value
BMI, kg/m^2	0.885	0.806–0.972	0.010
Smoking history, pack-years	0.993	0.977–1.009	0.367
[a]T4 level muscle index, cm^2/m^2	0.955	0.913–0.998	0.041
[b]T12 level muscle index, cm^2/m^2	0.980	0.856–1.121	0.766
GAP Score	1.450	1.169–1.760	0.001

Frailty (쇠약)

- **Age-related decline of physiological reserve resulting in an increased vulnerability to stressors**
- **A measure of functional age**
- **Common (12-50% of prevalence) in ILD**
- **Associated with dyspnea severity, increased risk of death**



Lancet 2019 ; 393: 2636-46



Lancet 2019 ; 394: 1365-75

Functional ageing in fibrotic interstitial lung disease: the impact of frailty on adverse health outcomes

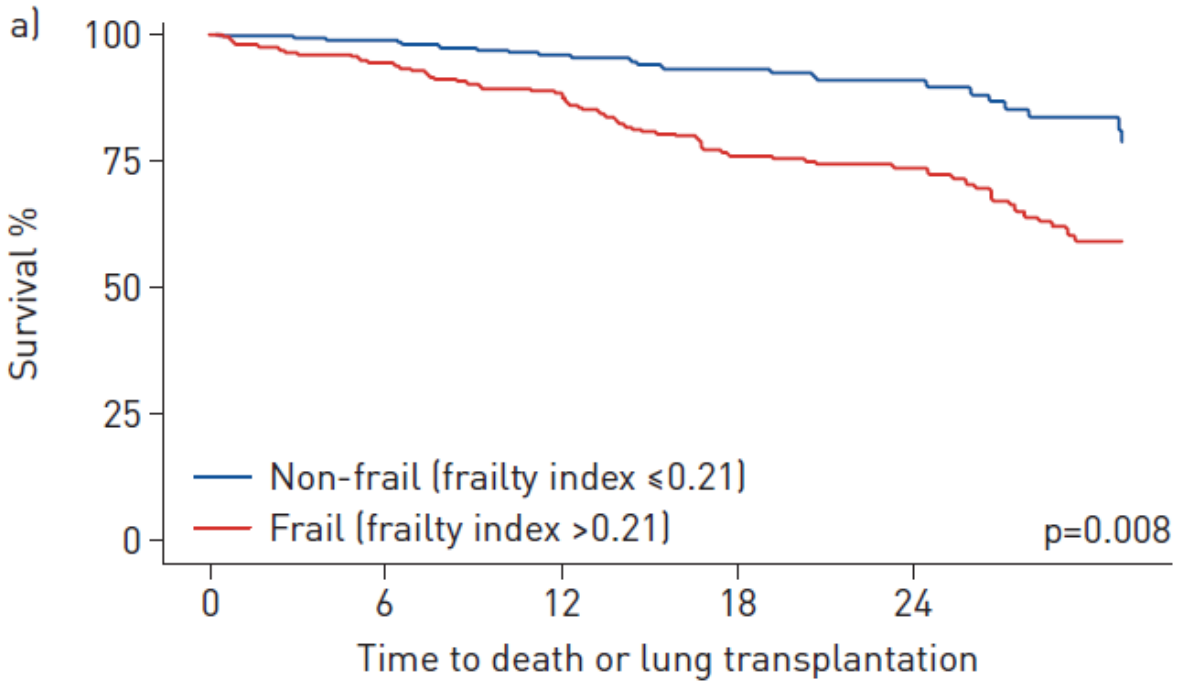
Sabina A. Guler[1,2,3], Joanne M. Kwan[1,2], Janice M. Leung[1,2], Nasreen Khalil[4], Pearce G. Wilcox[1] and Christopher J. Ryerson[1,2]

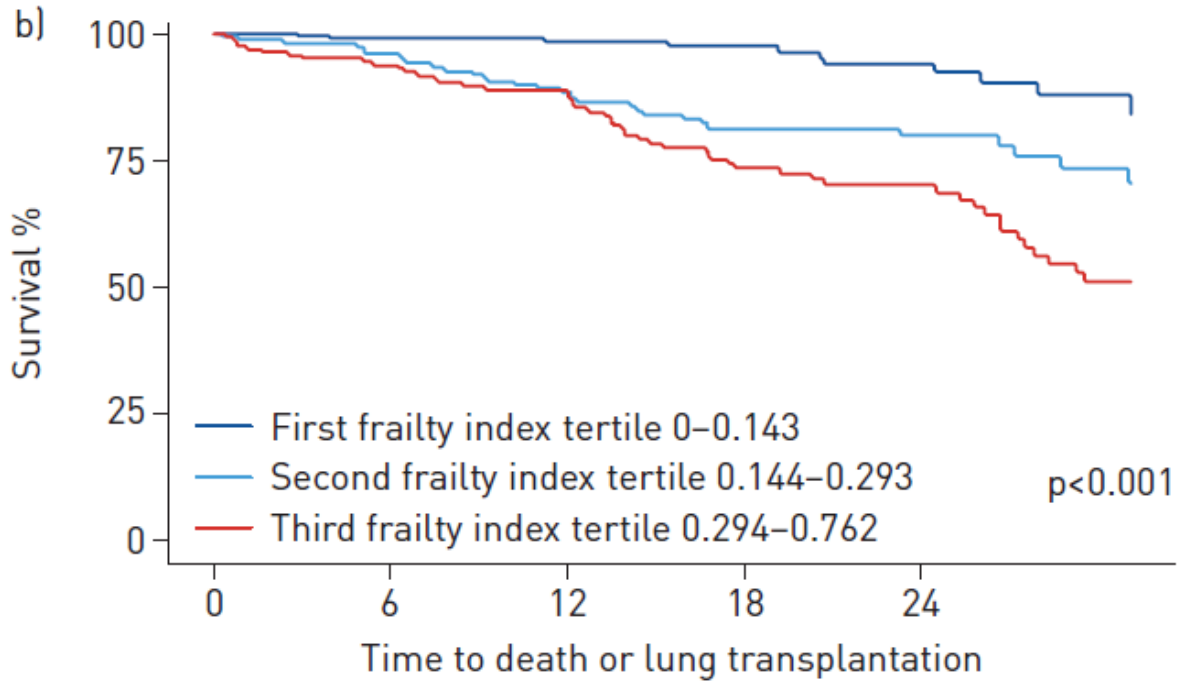
- ✓ **Outpatient ILD referral centre between July 2014 and July 2017**
- ✓ **540 patients with fibrotic ILD**
  IPF (n=100), systemic sclerosis-associated ILD (n=109), other CTD-ILD (n=118), chronic hypersensitivity pneumonitis (n=47) and 39 "other" ILDs 127 unclassifiable ILD
- ✓ **Frailty : Frailty index >0.21**

Eur Respir J 2020; 55: 1900647

	Unadjusted analysis		Adjusted for age, sex, FVC % pred, D_{LCO} % pred, IPF	
	Coefficient/IRR/HR (95% CI)	p-value	Coefficient/IRR/HR (95% CI)	p-value
Health-related quality of life (SGRQ)				
Frailty index	7.01 (6.04–7.98)	<0.0001	5.83 (4.81–6.84)	<0.0001
Co-FI	3.49 (2.25–4.72)	<0.0001	4.00 (2.79–5.22)	<0.0001
ISC-FI	5.25 (4.58–5.92)	<0.0001	4.41 (3.68–5.15)	<0.0001
Frail	21.6 (18.0–25.4)	<0.0001	18.0 (14.1–21.7)	<0.0001
Rate of all-cause hospitalisations				
Frailty index	1.03 (1.02–1.04)	<0.0001	1.03 (1.01–1.04)	<0.0001
Co-FI	1.02 (1.00–1.03)	0.01	1.03 (1.01–1.04)	0.003
ISC-FI	1.02 (1.01–1.02)	<0.0001	1.02 (1.01–1.03)	0.0001
Frail	2.25 (1.38–3.47)	<0.0001	1.97 (1.32–3.06)	0.002
Rate of respiratory-related hospitalisations				
Frailty index	1.03 (1.01–1.04)	0.0003	1.02 (1.01–1.04)	0.02
Co-FI	1.01 (0.99–1.03)	0.24	1.02 (1.00–1.04)	0.06
ISC-FI	1.02 (1.01–1.03)	<0.0001	1.01 (1.00–1.03)	0.03
Frail	2.01 (1.25–3.34)	0.003	1.63 (0.79–2.43)	0.09
Time to hospital discharge				
Frailty index	1.02 (1.00–1.03)	0.005	1.02 (1.00–1.03)	0.009
Co-FI	1.01 (0.99–1.02)	0.48	1.01 (0.99–1.03)	0.19
ISC-FI	1.01 (1.01–1.02)	0.001	1.01 (1.00–1.02)	0.004
Frail	1.56 (1.55–1.57)	0.01	1.35 (1.32–1.38)	0.048
Time to death				
Frailty index	1.03 (1.02–1.04)	<0.0001	1.02 (1.00–1.04)	0.02
Co-FI	1.01 (0.99–1.02)	0.46	1.02 (0.99–1.04)	0.26
ISC-FI	1.03 (1.02–1.04)	<0.0001	1.02 (1.00–1.03)	0.02
Frail	2.64 (2.31–3.02)	<0.0001	1.77 (1.50–2.08)	0.03

Eur Respir J 2020; 55: 1900647





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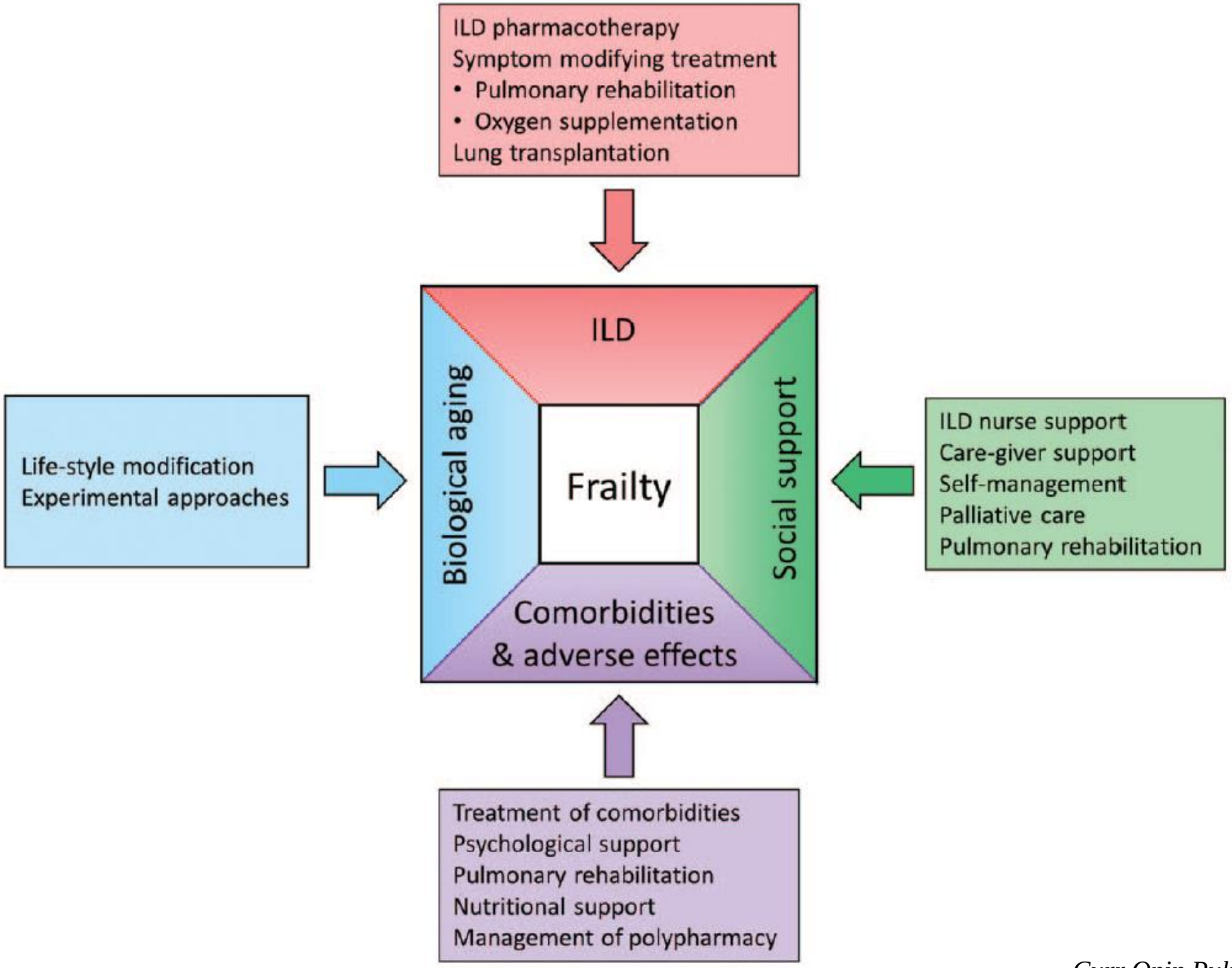
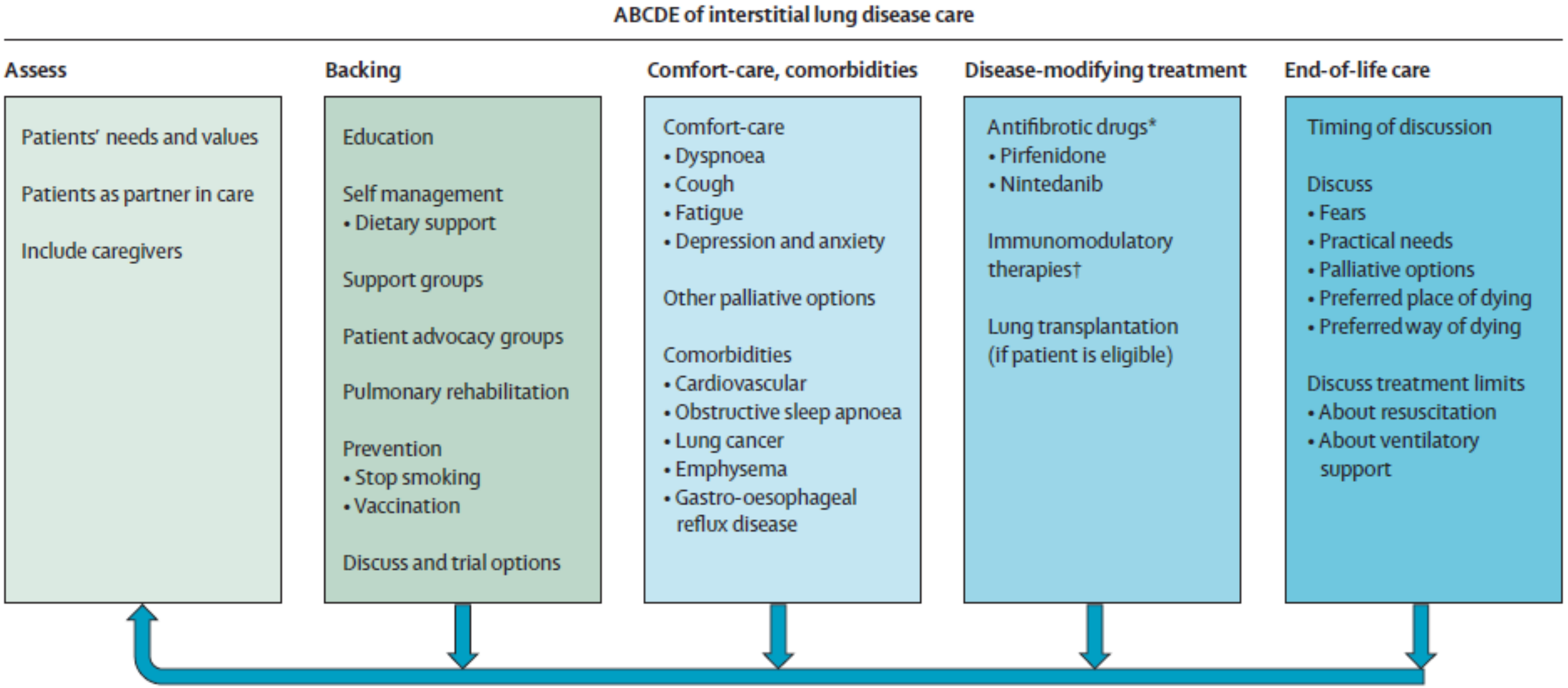


Curr Opin Pulm Med 2020; 26:449–456



Lancet Respir Med 2017; 5: 968–80

Summary

- **Symptoms and comorbidities in patients with ILD**
  - **Common**
  - **Health related quality of life and prognosis**
  - **Clinically significant to manage them**

- **Comprehensive care beyond pharmacological therapy**

경청해주셔서 감사합니다

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