



James Simmons, MD

8 Updates in Pulmonary Medicine 2021

JAMES SIMMONS, MD
GUEST EDITOR

**10 Obstructive Sleep Apnea Syndrome –
A Review for Primary Care Physicians and
Pulmonologists**

PARVATI SINGH, MD
ALICE BONITATI, MD

**14 The Clinical Utility of Cardiopulmonary
Exercise Testing**

EVAN J. SMITH, MD
ERIC J. GARTMAN, MD

**20 Updates on the Management of Cystic Fibrosis:
Development of Modulators and Advancement
of Antibiotic Therapies**

CHELSEA BOYD, MD
ROGER D. AUTH, MD
MICHAEL BLUNDIN, MD
DEBASREE BANERJEE, MD, MS

**26 Diagnosis and Management of Idiopathic
Pulmonary Fibrosis**

JULIA K. MUNCHEL, MD
BARRY S. SHEA, MD

30 Diagnosis of Pulmonary Hypertension

NAVNEET SINGH, MD
CHRISTOPHER J. MULLIN, MD, MHS

**36 The Evolving Continuum of Diagnosis in the
Modern Age of Non-Small Cell Lung Cancer**

DANIEL DUSTIN, DO
DOUGLAS MARTIN, MD

Updates in Pulmonary Medicine 2021

JAMES SIMMONS, MD
GUEST EDITOR

In the setting of the COVID-19 pandemic, pulmonary medicine has been brought to the forefront in the minds of many medical professionals over the past year. However, COVID-19 is only a small part of the vast array of pulmonary diseases that have affected and continue to impact Rhode Islanders. In this issue of the *Rhode Island Medical Journal*, pulmonologists from Rhode Island will review a variety of important and dynamic issues in pulmonary and sleep medicine, including common disease states with complicated management strategies and rare diseases that many readers are exposed to while practicing in Rhode Island and elsewhere. Our hope is this issue will improve both the specialist's and the general practitioner's ability and confidence in identifying, diagnosing, managing, and appropriately referring patients affected by these topics, so that we may all improve the lives of thousands of Ocean State patients.

Obstructive Sleep Apnea Syndrome

Obstructive Sleep Apnea Syndrome (OSAS) is a common and underdiagnosed disorder leading to significant morbidity for a variety of patients worldwide. Our knowledge of the risks of OSAS and benefits of therapy have continued to evolve, and **ALICE BONITATI, MD**, the Associate Director of the Lifespan Sleep Disorders Center in Rhode Island, and **PARVATI SINGH, MD**, provide a succinct but comprehensive up-to-date guide to the diagnosis and initial management of this disorder.

The Clinical Utility of Cardiopulmonary Exercise Testing

Cardiopulmonary exercise testing (CPET) is a functional and dynamic way to assess cardiopulmonary function at a patient's personal maximal exercise capacity. In many cases, the plethora of data generated can help differentiate complicated and unclear causes of dyspnea and exercise intolerance when used by experienced clinicians. **EVAN SMITH, MD**, along with **ERIC GARTMAN, MD**, Director of the Cardiopulmonary Exercise Training Laboratory at the Providence Veteran Affairs Medical Center, describe the components of CPET, as well as its varied indications to aid in evidence-based diagnosis, prognosis, and management of cardiopulmonary disease, including, for example, congestive heart failure, preoperative evaluation, and evaluation for organ transplant.

Updates on Cystic Fibrosis Treatments

Although cystic fibrosis (CF) is a rare disease, it still affects more than 70,000 people worldwide and leads to significant morbidity and mortality of multiple organ systems in many patients. As the therapies to manage CF have advanced and patients' life expectancies have increased, it has become a more chronic but complicated medical problem that can often be managed over decades with the appropriate multidisciplinary care. **DEBASREE BANERJEE, MD**, and **MICHAEL BLUNDIN, MD**, provide such care for many of the cystic fibrosis patients in Rhode Island, and, along with **CHELSEA BOYD, MD**, and **ROGER AUTH, MD**, they offer a review of the exciting recent changes to the management of cystic fibrosis in the age of personalized medicine, including a review of novel therapeutics that modulate the cystic fibrosis transmembrane regulator protein and changes to antibiotic management.

Diagnosis and Management of Idiopathic Pulmonary Fibrosis

Idiopathic pulmonary fibrosis (IPF) is the most common of the idiopathic interstitial pneumonias. Definitive diagnosis requires the exclusion of known causes of pulmonary fibrosis, aided by the multidisciplinary discussion involving pulmonologists, radiologists, and pathologists with expertise in the diagnosis of IPF and other forms of interstitial lung disease. **JULIA MUNCHEL, MD**, and **BARRY SHEA, MD**, provide an excellent review of the current recommendations for the diagnosis, prognostication, and management of patients with IPF, which focuses on anti-fibrotic therapy and early referral to lung transplant centers for those who are candidates.

Diagnosis of Pulmonary Hypertension

Pulmonary hypertension (PH) is a chronic disease of elevated pulmonary artery pressure that can result from pulmonary vascular diseases or complicate left heart and lung disease, while pulmonary arterial hypertension (PAH) is a rare pulmonary artery vasculopathy that leads to progressive right heart failure and death. Timely and accurate diagnosis of PH is paramount given the increased morbidity and mortality, but can be challenging given the nonspecific nature of the presenting symptoms and the many potential causative or contributing conditions. Although right heart catheterization is required for diagnosis and early referral to a PH expert

center, such as the Rhode Island Hospital Pulmonary Hypertension Center, is strongly recommended, it is an important and increasingly common problem for all RI healthcare providers to consider and care for. To that end, **NAVNEET SINGH, MD**, and **CHRISTOPHER MULLIN, MD**, a pulmonary hypertension specialist practicing in RI, provide a review of the complicated workup of PH, based on the current medical knowledge and significant local experience.

The Evolving Continuum of Diagnosis in the Modern Age of Non-Small Cell Lung Cancer

Although lung cancer is the leading cause of cancer-related death in the United States, there has been significant advancement in the diagnosis and treatment of non-small cell lung cancer (NSCLC) over the past couple of decades. Improvements in diagnostic evaluation and biopsy techniques coupled with advances in targeted therapies with newer drug targets are giving patients and their families

more hope in the face of this challenging disease, but this, in turn, leads to new challenges navigating increasingly complex decision-making for the healthcare providers. **DANIEL DUSTIN, DO**, and **DOUG MARTIN, MD**, provide a concise overview of the current best practices for workup and management of NSCLC from the pulmonary viewpoint, while also noting emergent complications based on recent data and their personal experiences caring for patients with lung cancer in RI.

In conclusion, we hope this compilation will enhance your knowledge of and interest in some of the many important pulmonary diseases seen in Rhode Island patients and the world at large.

Guest Editor

James Simmons, MD, Assistant Professor of Medicine, Alpert Medical School of Brown University; Pulmonary and Critical Care Physician, The Miriam Hospital, Providence, RI.

Obstructive Sleep Apnea Syndrome – A Review for Primary Care Physicians and Pulmonologists

PARVATI SINGH, MD; ALICE BONITATI, MD

ABSTRACT

Obstructive sleep apnea syndrome (OSAS) is a prevalent sleep disorder that leads to excessive daytime sleepiness and poor quality of life. OSAS is characterized by intermittent hypoxia and sleep fragmentation and is associated with increased risk of cardiovascular and neurocognitive disorders. The focus of our article is to discuss the approach to diagnosis and management.

KEYWORDS: obstructive sleep apnea, apnea, polysomnography, AHI, positive airway pressure therapy

EPIDEMIOLOGY AND CLINICAL MANIFESTATIONS

Obstructive sleep apnea (OSA) is a sleep-related breathing disorder that is defined by either partial or complete collapse of the airway that interrupts ventilation.¹ These interruptions in breathing during sleep can result in intermittent hypoxia, sleep fragmentation, and lack of restorative sleep.¹ OSAS refers to symptomatic obstructive sleep apnea.

Fatigue, daytime sleepiness, and poor quality of life are hallmark symptoms of OSAS. Other common symptoms include headaches, awakenings with gasping or choking sensation, concentration and memory problems, irritability, and depression.¹ Additionally, OSAS is associated with increased risk of hypertension, atrial fibrillation, myocardial infarction, pulmonary hypertension, insulin resistance, and stroke.² This risk is primarily applicable to patients with moderate to severe disease. A 2021 meta-analysis found that OSA was associated with an increased risk for cardiac and all-cause mortality.³

There is data suggesting that OSAS increases the risk of developing dementia and cancer.² A cohort study found that patients with sleep disordered breathing developed mild cognitive impairment at an earlier age than those who did not have self-reported sleep disordered breathing.⁴ In a prospective study of 298 women 65 years or older without dementia, those with OSA were more likely to develop mild cognitive impairment or dementia (45% vs 35%, $p=0.02$, adj. odds ratio 1.8).²¹ With regards to malignancy, the theory is that repetitive hypoxic episodes lead to a change in gene expression for angiogenesis.² A study that followed patients from the Wisconsin Sleep Cohort for 22 years found that as the severity of OSA increased the cancer mortality also increased.⁵

It is estimated that more than 1 billion people globally have some degree of OSA.⁶ Obesity is a major risk factor, partially explaining the increased prevalence of the disorder in our society. Weight gain of 10% can lead to a six-fold increase in odds of developing OSA.¹ Other risk factors include age, male gender, tonsillar hypertrophy, and craniofacial abnormalities that narrow the upper airway.⁷ It is important to note that approximately 25% of patients with OSA in the U.S. are non-obese.¹⁶ Ethnicity is one factor implicated in OSA in non-obese individuals. In addition, non-obese OSA represents its own phenotype, exhibiting some differences in clinical characteristics such as lower arousal threshold and often lesser tolerance of positive pressure therapy.¹⁶

DIAGNOSIS

Patients to consider for testing are those with any of the above signs or symptoms. Snoring in conjunction with suggestive OSA symptom(s) or comorbidities is an indication for testing. On exam, patients may have a wide neck, large tongue, large adenoids/tonsils, and a Mallampati score of III-IV.⁷ Questionnaires can be helpful in identifying patients who should be screened for OSAS. A score of ≥ 10 on the Epworth Sleepiness Scale and/or a score ≥ 3 on STOP-BANG questionnaire are concerning for possible sleep apnea.⁷ The STOP-BANG screening tool that asks yes or no questions about snoring, fatigue, observed apneas, hypertension, BMI, age, neck circumference, and gender has ~90–93% sensitivity for sleep apnea.¹ While useful, this and other screening tools have not been validated in all populations, such as in patients undergoing bariatric surgery, in whom excessive daytime sleepiness may be lacking.²⁵ OSA is highly prevalent in the bariatric patient population and there is increased risk of peri- and postoperative complications if sleep apnea is not monitored and treated. Therefore, all patients should undergo testing to determine if they have sleep apnea and start treatment if the sleep apnea is found to be significant.

Polysomnography (PSG) or home sleep testing is generally required to diagnose OSAS. An all-night in-laboratory PSG involves use of EEG, EOG (electrooculography), EMG, pressure sensors to detect air flow, EKG, and chest/abdomen belts to detect respiratory effort.¹ Despite PSGs being the gold standard test, there are drawbacks of cost, possible lack of insurance coverage, and lower patient acceptance compared to home testing.

Home sleep apnea testing (HSAT) use has been on the rise, due to benefits of convenience, lower cost, and increased access to evaluation, as well as improved quality of this testing.⁸ Compared to PSG, HSAT does not utilize EEG or EMG and therefore actual sleep time is not known.¹ HSAT should be used when there is a high pretest probability for OSA, there are no severe comorbidities and no concern for additional sleep disorders.¹ HSATs can underestimate severity or miss OSA. False negative rate of this test is approximately 17%.¹ Thus, if HSAT is negative then the patient should generally complete a formal PSG.¹

One ambulatory sleep study device that is gaining traction is the WatchPAT, a peripheral arterial tonometer. The WatchPAT measures apnea or hypopnea by using an algorithm that utilizes data on the changes in peripheral arterial blood volume, desaturations on pulse oximetry, and changes in heart rate.⁹ A meta-analysis showed that WatchPAT's respiratory indexes did correlate with scoring from PSGs.⁹ The peripheral arterial tonometry has a positive predictive value of 76% and negative predictive value of 83%.¹ Currently however, a PSG or HSAT is required to initiate therapy.

The tests mentioned determine the apnea-hypopnea index (AHI) score and help guide treatment options for OSA.⁷ AHI is the number of hypopnea/apnea events per an hour and is used for classification of OSA severity. In adults, AHI 5-14.9 is mild OSA, AHI 15-29.9 is moderate OSA, and AHI \geq 30 is severe OSA. Of note, this classification system does not account for other factors that could contribute to severity of OSA, such as the level of desaturation, degree of sleep fragmentation, or level of sympathetic system activation.¹⁷

TREATMENT

Lifestyle changes and conservative measures

Lifestyle changes can improve OSA and in those with mild disease and symptoms can sometimes be the primary form of management. The following are beneficial:

1. Weight loss lowers severity of OSA,¹³ but especially in moderate to severe disease is often not curative.
2. Patients should limit alcohol, opiate, and benzodiazepine use.
3. Smoking cessation may help as well. Nicotine is thought to increase upper airway muscle collapse due to muscle relaxation and increased sleep fragmentation.¹³
4. Many patients have worse AHI scores in the supine position in part due to airway closure due to tongue relaxation. It has been shown that sleeping in the lateral decubitus position can decrease sleepiness and AHI scores.¹³ There are many positional devices that can be used to help patients sleep off their back.
5. Treatment of nasal congestion to improve upper airway patency.

Positive Airway Pressure Therapy (PAP)

The mainstay of OSA treatment is PAP therapy, in which positive pressure is applied to keep the upper airway patent during sleep, thereby reducing apneas and hypopneas. PAP therapy can be either CPAP, APAP (auto-titrating), or BiPAP (bilevel). According to the American Academy of Sleep Medicine (AASM) clinical practice guidelines, PAP therapy is recommended for patients with excessive sleepiness.¹⁰ There have been 38 randomized control trials that have shown that PAP decreases excessive sleepiness with minimal side effects.¹⁰ Effective PAP pressures can be determined during split PSG testing, in which pressures are titrated during the second half of the night. Positive pressure titration in the sleep center is recommended for patients with CHF, COPD, central sleep apnea, and obesity hypoventilation syndrome.¹ Otherwise, APAP can be prescribed. APAP is set over a range of PAP pressures and the unit titrates the pressure to achieve the lowest AHI score. Once the patient is using APAP for a period of time, the patient's sleep medicine provider reviews efficacy of therapy and makes additional adjustments to settings if needed.

Per the AASM guidelines, there is a conditional recommendation of prescribing PAP therapy to patients with diagnosed OSA with HTN or impaired sleep-related quality of life.¹⁰ There have been five randomized control trials showing that PAP therapy can lower blood pressure, though a meta-analysis did not support this.¹⁰ Similarly, in terms of impaired sleep-related quality of life, a meta-analysis did not support the positive benefits seen in 19 randomized control trials.¹⁰

Additionally, the AASM guidelines list that there is not enough evidence on the use of PAP therapy for asymptomatic OSA patients.¹⁰ There is mixed data regarding whether implementation of PAP therapy reverses the increased risk of cardiovascular disease or mortality. Observational studies have shown a positive response to PAP therapy for cardiovascular outcomes, while four randomized control trials have not confirmed, but have not excluded benefit in this regard.¹⁰ Negative results may be related to exclusion of patients with more significant cardiovascular disease and the relatively low PAP adherence in these randomized trials.¹ A recent study found that the degree of heart rate increase in relation to apneas/hypopneas was a predictor of poor cardiovascular outcomes, and perhaps these patients should be included in future randomized trials.²² In a recent subgroup analysis of a large RCT, it was found that patients with CAD who used CPAP for more than 4 hours a night had lower rates of cardiovascular or neurovascular events compared to patients who used it for less than 4 hours a night.²⁴ About 20% of OSA patients have pulmonary hypertension, and small studies have shown that CPAP therapy lowers right ventricular and pulmonary artery pressures.²³

Adherence to PAP therapy is a significant issue for patients with OSAS. To improve compliance, finding a well-fitting

and comfortable interface and using in-line humidification can be helpful.¹⁰ Despite these adjustments, PAP adherence can still be poor, especially in those who require higher pressures.¹² A ramp function with which the starting pressure is gradually increased can also help with comfort.¹² It has been recently shown that remote electronic monitoring of PAP use by patients and their providers can lead to improved overall compliance with therapy. Over the past one to two decades there have been significant improvements in PAP technology, leading to improved comfort with therapy.

Other Therapies for OSA

Other therapies for OSAS include oral appliances, upper airway surgery, and hypoglossal nerve stimulation.

Mandibular Advancement Devices are often a good alternative to PAP therapy for mild to moderate OSAS. The mandibular device causes the mandible to jut forward, advancing the tongue and lifting the palate thereby reducing airway collapse.¹⁴ One retrospective study of OSA patients with mild to severe disease found that a mandibular device led to 37% of patients having resolution of their OSA and 64% of patients having their AHI score cut in half.¹⁴ However, the response to the mandibular device was not as profound in patients with severe OSA.¹⁴

Lastly, various surgeries have been used to treat OSA. The data for this treatment option is mostly limited to case series and a handful of RCTs. There is no RCT comparing PAP therapy against surgical interventions for OSA treatment. Two RCTs have compared upper airway surgery with conservative management in patients who did not tolerate PAP or mandibular advancement devices.^{19,20} The SKUP3 RCT trial found that uvulopalatopharyngoplasty (UPPP) reduced AHI on average from 53.3 to 21.1, though a few patients had an increase in AHI after surgery.¹⁹ Similarly, the SAMS RCT trial found that those who had UPPP with radiofrequency ablation to reduce tongue size had average drop in AHI from 47.9 to 20.8.²⁰ Only 28% of patients had resolution of OSA.²⁰ Other surgical interventions include tonsillectomy (usually performed with UPPP), genioglossus advancement, and maxillo-mandibular advancement. Generally, in select patients with certain anatomical abnormalities who do not tolerate PAP or mandibular devices, surgical intervention is an option. Surgery can reduce the severity of OSA and in well-selected patients it can sometimes completely treat sleep apnea.

Hypoglossal nerve stimulation (HNS) is a newer therapy that stimulates the nerve to act on the genioglossus muscle during sleep to help open the upper airway.¹ A cohort study in 2014 found the hypoglossal nerve stimulator lowered the median AHI score by 68% in 12 months and also decreased level of daytime sleepiness in OSA patients.¹⁵ HNS is considered if the patient fails or doesn't tolerate PAP therapy, does not have concentric collapse of the upper airway on drug-induced sleep endoscopy (DISE), and there is no anatomical obstruction, BMI \leq 35 kg/m², and AHI is 15–65.¹⁸

CONCLUSION

OSAS is a highly prevalent sleep disorder that can negatively affect quality of life and is linked to cardiovascular disorders and neurocognitive abnormalities. Diagnosis is generally made with PSG or home-sleep testing. Primary treatment for symptomatic OSA, especially if moderate or severe, is usually with positive airway pressure therapy, but other therapies are available and evolving. PAP therapy has been shown to improve excessive daytime sleepiness, AHI score, and blood pressure. It is likely that there are benefits for primary and secondary prevention of cardiovascular events including stroke, but results of randomized controlled trials are mixed and there are large ongoing studies examining this topic.

References

1. Lee JJ, Sundar KM. Evaluation and Management of Adults with Obstructive Sleep Apnea Syndrome. *Lung*. 2021 Apr;199(2):87-101.
2. Lim DC, Pack AI. Obstructive Sleep Apnea: Update and Future. *Annu Rev Med*. 2017 Jan 14;68:99-112.
3. Heilbrunn ES, Ssentongo P, Chinchilli VM, Oh J, Ssentongo AE. Sudden death in individuals with obstructive sleep apnoea: a systematic review and meta-analysis. *BMJ Open Respir Res*. 2021 Jun;8(1):e000656.
4. Osorio RS, Gumb T, Pirraglia E, Varga AW, Lu SE, Lim J, Wohleber ME, Ducca EL, Koushyk V, Glodzik L, Mosconi L, Ayappa I, Rapoport DM, de Leon MJ. Alzheimer's Disease Neuroimaging Initiative. Sleep-disordered breathing advances cognitive decline in the elderly. *Neurology*. 2015 May 12;84(19):1964-71.
5. Nieto FJ, Peppard PE, Young T, Finn L, Hla KM, Farré R. Sleep-disordered breathing and cancer mortality: results from the Wisconsin Sleep Cohort Study. *Am J Respir Crit Care Med*. 2012 Jul 15;186(2):190-4.
6. Benjafield AV, Ayas NT, Eastwood PR, Heinzer R, Ip MSM, Morrell MJ, Nunez CM, Patel SR, Penzel T, Pépin JL, Peppard PE, Sinha S, Tufik S, Valentine K, Malhotra A. Estimation of the global prevalence and burden of obstructive sleep apnoea: a literature-based analysis. *Lancet Respir Med*. 2019 Aug;7(8):687-698.
7. Slowik J, Collen J. 2020, Dec 3. Obstructive Sleep Apnea. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2021 Jan. Available from: Obstructive Sleep Apnea - StatPearls - NCBI Bookshelf (nih.gov)
8. Billings ME, Pendharkar SR. Alternative Care Pathways for Obstructive Sleep Apnea and the Impact on Positive Airway Pressure Adherence: Unraveling the Puzzle of Adherence. *Sleep Med Clin*. 2021 Mar;16(1):61-74.
9. Yalamanchali S, Farajian V, Hamilton C, Pott TR, Samuelson CG, Friedman M. Diagnosis of obstructive sleep apnea by peripheral arterial tonometry: meta-analysis. *JAMA Otolaryngol Head Neck Surg*. 2013 Dec;139(12):1343-50.
10. Patil SP, Ayappa IA, Caples SM, Kimoff RJ, Patel SR, Harrod CG. Treatment of Adult Obstructive Sleep Apnea with Positive Airway Pressure: An American Academy of Sleep Medicine Clinical Practice Guideline. *J Clin Sleep Med*. 2019 Feb 15;15(2):335-343.
11. Sánchez-de-la-Torre M, Sánchez-de-la-Torre A, Bertran S, Abad J, Duran-Cantolla J, Cabriada V, Mediano O, Masdeu MJ, Alonso ML, Masa JE, Barceló A, de la Peña M, Mayos M, Coloma R, Montserrat JM, Chiner E, Perelló S, Rubinós G, Mínguez O, Pascual L, Cortijo A, Martínez D, Aldomà A, Dalmasas M, McEvoy RD, Barbé F; Spanish Sleep Network. Effect of obstructive sleep apnoea and its treatment with continuous positive airway pressure on the prevalence of cardiovascular events in patients with acute coronary syndrome (ISAACC study): a randomised controlled trial. *Lancet Respir Med*. 2020 Apr;8(4):359-367.

12. Killick R, Marshall NS. The Impact of Device Modifications and Pressure Delivery on Adherence. *Sleep Med Clin*. 2021 Mar;16(1):75-84.
13. Kaleelullah RA, Nagarajan PP. Cultivating Lifestyle Transformations in Obstructive Sleep Apnea. *Cureus*. 2021 Jan 26;13(1):e12927.
14. Sutherland K, Takaya H, Qian J, Petocz P, Ng AT, Cistulli PA. Oral Appliance Treatment Response and Polysomnographic Phenotypes of Obstructive Sleep Apnea. *J Clin Sleep Med*. 2015 Aug 15;11(8):861-8.
15. Strollo PJ Jr, Soose RJ, Maurer JT, de Vries N, Cornelius J, Froymovich O, Hanson RD, Padhya TA, Steward DL, Gillespie MB, Woodson BT, Van de Heyning PH, Goetting MG, Vanderveken OM, Feldman N, Knaack L, Strohl KP; STAR Trial Group. Upper-airway stimulation for obstructive sleep apnea. *N Engl J Med*. 2014 Jan 9;370(2):139-49.
16. Gray EL, McKenzie DK, Eckert DJ. Obstructive Sleep Apnea without Obesity Is Common and Difficult to Treat: Evidence for a Distinct Pathophysiological Phenotype. *J Clin Sleep Med*. 2017 Jan 15;13(1):81-88.
17. Rapoport DM. POINT: Is the Apnea-Hypopnea Index the Best Way to Quantify the Severity of Sleep-Disordered Breathing? Yes. *Chest*. 2016 Jan; 149(1):14-6.
18. Steffen A, Heiser C, Galetke W, Herkenrath SD, Maurer JT, Gunther E, Stuck BA, Woehrle H, Lohler J, Randerath W. Hypoglossal nerve stimulation for obstructive sleep apnea: updated position paper of the German Society of Oto-Rhino-Laryngology, Head and Neck Surgery. *Eur Arch Otorhinolaryngol*. 2021 Jun 21.
19. Browaldh N, Nerfeldt P, Lysdahl M, Bring J, Friberg D. SKUP3 randomised controlled trial: polysomnographic results after uvulopalatopharyngoplasty in selected patients with obstructive sleep apnoea. *Thorax*. 2013 Sep; 68(9): 846-53.
20. MacKay S, Carney As, Catchside PG, Chai-Coetzer CL, Chia M, Cistulli PA, Hodge JC, Jones A, Kaambwa B, Lewis R, Ooi EH, Pinczel AJ, McArdle N, Rees G, Singh B, Stow N, Weaver EM, Woodman RJ, Woods CM, Yeo A, McEvoy RD. Effect of Multilevel Upper Airway Surgery vs Medical Management on the Apnea-Hypopnea Index and Patient-Reported Daytime Sleepiness Among Patients with Moderate or Severe Obstructive Sleep Apnea: The SAMS Randomized Clinical Trial. *JAMA*. 2020 Sep 22;324(12):1168-1179.
21. Yaffe K, et al. *JAMA*. 2011;306(6):613-619.
22. Azarbarzin A, Sands SA, Younes M, Taranto-Montemurro L, Sofer T, Vena D, Alex RM, Kim SW, Gottlieb DJ, White DP, Redline S, Wellman A. The Sleep Apnea-Specific Pulse-Rate Response Predicts Cardiovascular Morbidity and Mortality. *Am J Respir Crit Care Med*. 2021 Jun 15;203(12):1546-1555.
23. Kholdani C, Fares WH, Mohsenin V. Pulmonary hypertension in obstructive sleep apnea: is it clinically significant? A critical analysis of the association and pathophysiology. *Pulm Circ*. 2015 Jun;5(2):220-7.
24. Peker Y, Thunström E, Glantz H, Eulenburg C. Effect of Obstructive Sleep Apnea and CPAP Treatment on Cardiovascular Outcomes in Acute Coronary Syndrome in the RICCADSA Trial. *J Clin Med*. 2020 Dec 15;9(12):4051.
25. Sharkey K, et al Predicting OSA among women candidates for bariatric surgery. *J Women's Health*. 2010 19(10):1833-1841.

Authors

Parvati Singh, MD, Sleep Medicine Fellow, University of Pennsylvania.

Alice Bonitati, MD, Associate Professor of Medicine, Clinician Educator, Division of Pulmonary, Critical Care and Sleep Medicine, Brown University.

Correspondence

Alice Bonitati, MD

Rhode Island Hospital

Division of Pulmonary, Critical Care and Sleep Medicine

593 Eddy Street (APC 7)

Providence, RI 02903

401-444-2670

Fax 401-444-5493

Abonitati@lifespan.org

The Clinical Utility of Cardiopulmonary Exercise Testing

EVAN J. SMITH, MD; ERIC J. GARTMAN, MD

KEYWORDS: cardiopulmonary exercise testing, physiology, stress testing, oxygen consumption (VO₂)

GLOSSARY

AT – Anaerobic threshold, the point at which oxygen delivery to exercising muscle can no longer meet demands and lactic acid begins to accumulate

VO₂ – oxygen consumption per minute, expressed in L/min and mL/kg/min

VO₂^{peak} – Highest VO₂ obtained during an exercise test. If a further increase in workload does not lead to further increase in VO₂, i.e. there is a plateau in VO₂, this is referred to as **VO₂^{max}**.

VO₂^{reserve} – Difference between resting VO₂ and VO₂^{max}.

VCO₂ – Carbon dioxide production, L/min

VE – Minute ventilation, L/min

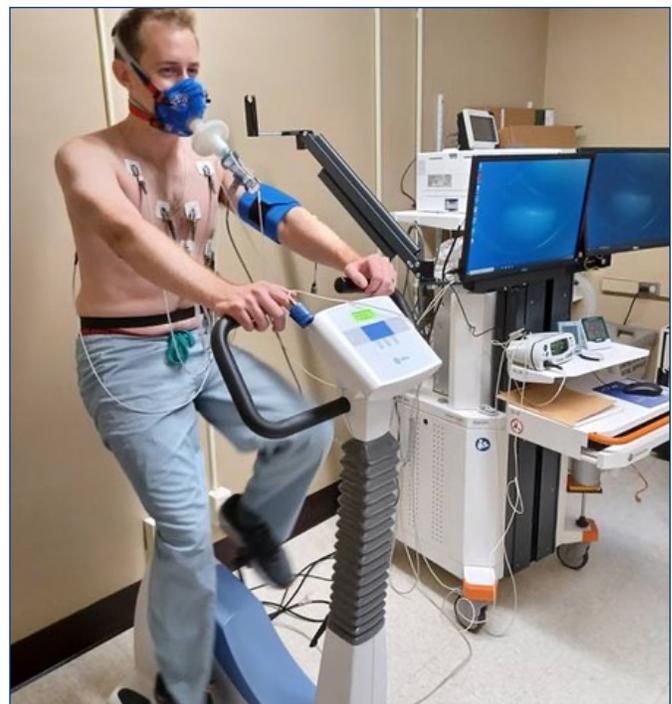
VE/VCO₂ – Ratio of minute ventilation to CO₂ production (how much one is breathing to ventilate off a given amount of CO₂), a measure of ventilatory efficiency

INTRODUCTION

Cardiopulmonary exercise testing (CPET) can be conducted in several ways, but most commonly is performed as a progressive incremental exercise test that concludes at exhaustion at maximal exercise capacity. For several reasons, the most important being safety, the test generally is done utilizing a cycle ergometer that has the ability to ramp the work rate over time. During the exam, the patient has extensive safety monitoring – including continuous electrocardiogram (ECG), pulse oximetry, and frequent blood pressure recordings. A physician typically is in attendance for the duration of the test. Additionally, the patient has all inhaled and exhaled gas analyzed – with the ability to determine oxygen consumption (VO₂), carbon dioxide elimination (VCO₂), tidal volumes, and respiratory flow curves. Before and directly after the test serial spirometry is performed to assess baseline pulmonary function and assess for exercise-induced airway disorders, respectively. See **Figure 1** for typical CPET laboratory set-up and equipment.

It is well known that static measures of pulmonary and cardiac function (such as pulmonary function testing (PFT)

Figure 1. Typical CPET laboratory set-up using a cycle ergometer. The monitoring equipment includes continuous ECG, pulse oximetry, sphygmomanometer, flow sensor, and gas analyzer (interface can either be facemask or mouthpiece/noseclip). Also, the equipment has the ability to perform standalone spirometry.



and echocardiography) do not always relate well to dynamic measures during exertion.¹ While other modalities of stress testing are well-suited for a limited evaluation (e.g. a cardiac stress test for ischemia), the extensive cardiopulmonary data obtained by CPET has the potential to determine the overriding factor or system limiting maximal exercise (e.g. cardiac, ventilatory, systemic vascular, mitochondrial, deconditioning or psychological). Further, given that it does not have artificial test stopping points (e.g. HR endpoints), a full evaluation of the cardiopulmonary system can be obtained. Many of performance measures that are obtained during the test are able to be reported as percent predicted using published equations – such as VO₂^{peak}, work rate, and certain ventilation parameters.

While overwhelmingly the most common indication for CPET is unexplained dyspnea on exertion, this review

will examine the evidence supporting other valuable uses for CPET, including in heart failure, evaluation for cardiac transplant, and preoperative evaluation (Table 1).

Table 1. Indications for CPET referral. Adapted from ATS/ACCP Statement, 2001⁴

Disease state	Indication
Dyspnea on Exertion	Unexplained dyspnea
Congestive Heart Failure	Guide transplant referral Prognostication Response to medical therapy
Pre-operative, general surgery	Predictive of post-operative complications and mortality Guide post-operative level of care Inform shared decision making
Pre-operative, lung resection	Identify those who will tolerate resection
Lung volume reduction surgery (LVRS)	Identify those most likely to benefit from LVRS Measure functional improvement post-operative
Asthma	Identification of exercise-induced bronchospasm Identification of non-ventilatory exercise limitation
Cystic Fibrosis	Prognostication
COPD	Identification of non-ventilatory exercise limitation Early identification of group 3 pulmonary hypertension
Pulmonary Hypertension	Identify Etiology Prognostication Evaluate response to treatment
Rehabilitation	Determine safety pre-rehabilitation Determine precise rehabilitation prescription Evaluate response to rehabilitation

DYSPNEA EVALUATION

The most common indication for CPET is unexplained dyspnea or dyspnea out of proportion to disease severity demonstrated on other testing. Unexplained dyspnea or exercise intolerance is considered a Class I indication for CPET referral.² Unexplained dyspnea is largely divided into two categories – patients with no obvious cause on routine testing and patients with multiple potential causes. It is most often the case that patients are referred for CPET after they have had a fairly significant evaluation that has been unrevealing – including PFTs, radiographic imaging, echocardiography, and/or cardiac stress testing. Common etiologies of symptoms that may be suggested through CPET include limits on ventilation, exercise-induced bronchoconstriction, cardiac ischemia, heart failure, pulmonary hypertension, and peripheral vascular disease. Additionally, CPET can potentially identify non-cardiopulmonary limitations such as

pathologic breathing patterns, obesity, and deconditioning.³ Assuming a maximal test is performed, the comprehensive nature of a CPET can provide reassurance to a patient and potentially limit further diagnostic testing. Likewise, when a defined etiology of exercise limitation is identified, CPET can guide further therapy and investigations – or help determine which system warrants further therapeutic attention or testing in a patient with several known conditions.⁴

CPET also can be helpful in the evaluation of disability due to exertional symptoms. Often, job-related or exertional complaints are out of proportion to routine testing results used for disability determination (such as PFTs or echocardiography), making it difficult for such patients to receive compensation.⁵ Maximal CPET can provide an objective measure of work capacity and possesses the ability to differentiate poor volitional effort from a true physiologic impairment – and may be helpful in select workman's compensation cases.¹

CONGESTIVE HEART FAILURE

Outside of the evaluation of dyspnea, CPET has been studied most robustly in the realm of congestive heart failure. There are several roles for comprehensive exercise testing in therapeutic management of heart failure with or without reduced ejection fraction, including prognostication and evaluation for transplant.

CPET has been studied extensively in the evaluation for eligibility for cardiac transplantation. Using CPET to evaluate patients prior to transplant is considered a class IA indication², with $VO_{2\text{peak}}$ being the variable most often utilized. In one prospective study of patients referred for cardiac transplant, $VO_{2\text{peak}}$ of 14cc/kg/minute was used as a cut-off for transplant surgery. Those who were referred for cardiac transplant with $VO_{2\text{peak}} > 14\text{cc/kg/min}$ who did not receive a transplant had a similar 1- and 2-year survival (94% and 84% respectively) to those who underwent transplant. Those with $VO_{2\text{peak}}$ less than that cut-off who did not receive a transplant due to non-cardiac reasons had a significantly lower survival at 1 and 2 years (47% and 32%).⁶ While this landmark study was not randomized, and there is a question of conditions that prohibited transplant as contributing to mortality, in practice a cut-off of 14cc/kg/min $VO_{2\text{peak}}$ is used to determine the eligibility for cardiac transplant. Further, those who are re-evaluated while awaiting their transplant who are able to increase their $VO_{2\text{peak}}$ by at least 2cc/kg/min to at least 12cc/kg/minute are able to be safely removed from the transplant list and show excellent survival (85–100% at 2 years).⁷

It follows that those with higher levels of fitness, as measured by $VO_{2\text{peak}}$, are more likely to have better outcomes. This variable has been studied in prognosticating heart failure with both preserved and reduced ejection fraction. Using an outcome of transplant and mechanical support-free

survival, patients can be stratified into groups based on their $VO_{2\text{peak}}$, corresponding to Weber class, a functional class analogous to NYHA class. The most fit (defined as $>20\text{cc/kg/min}$) exhibited a 3-year survival of 97%, which was similar to those in the next highest quartile ($16\text{--}20\text{cc/kg/min}$). Three-year survival decreased further as $VO_{2\text{peak}}$ declined (83% with a $VO_{2\text{peak}}$ of $10\text{--}16\text{cc/kg/min}$ and 64% for those $<10\text{cc/kg/min}$) (Table 2).

Similar to what has been seen in those awaiting heart transplant, patients with systolic heart failure are able to improve their risk of mortality and hospitalization by undergoing exercise training programs. In the large HF-ACTION trial, those undergoing a supervised exercise program were able to increase their $VO_{2\text{peak}}$ an average of 4%⁹; with other studies demonstrating that formalized exercise programs can increase $VO_{2\text{peak}}$ by 10%–18%.^{10,11} In the HF-ACTION trial, $VO_{2\text{peak}}$ percent predicted $VO_{2\text{peak}}$ and exercise duration had the strongest associations with mortality in both systolic and diastolic heart failure.⁹

Table 2. Survival in Congestive Heart Failure stratified by $VO_{2\text{peak}}$. Adapted from Luiz, et al⁸

$VO_{2\text{peak}}$	3-year event free survival
$>20\text{cc/kg/min}$ (Weber Class A)	97%
$16\text{--}20\text{cc/kg/min}$ (Weber Class B)	94%
$10\text{--}16\text{cc/kg/min}$ (Weber Class C)	83%
$<10\text{cc/kg/min}$ (Weber Class D)	64%

PREOPERATIVE USE OF CPET IN GENERAL SURGERY

The use of CPET in preoperative risk stratification has been extensively studied. However, unlike in heart failure, the studies in preoperative risk assessment are more heterogeneous given the different outcome measures used and the variability inherent in various surgical populations (Table 3).

Many studies have demonstrated that low $VO_{2\text{peak}}$, early anaerobic threshold, and elevated ratio of maximal ventilation to CO_2 production during exercise (VE/VCO_2) can predict operative complications and mortality.^{12,13,14} Identifying those at higher operative risk via the objective outcomes

Table 3. Utility of CPET parameters in predicting post-operative complications and survival. Adapted from Moran, et al¹⁵

	AT	$VO_{2\text{peak}}$	VE/VCO_2
Hepatic	Strong Association	Equivocal	No association
AAA	Equivocal	Equivocal	Limited Association
Colorectal	Strong Association	Strong Association	Equivocal
Pancreatic	Limited association	Equivocal	Strong Association
Bariatric/Upper GI	No association	No association	No association
Renal Transplant	No association	No association	No association

from CPET can provide valuable information for appropriate patient selection for surgery and when discussing operative risk with patients.

A large systematic review¹⁵ of 37 studies, encompassing 7852 patients, identified which variables were most predictive of poor outcomes relative to a given operation. For hepatic transplant or resection, early anaerobic threshold was most predictive of mortality with a value $<9.9\text{cc/kg/minute}$ predicting 30-day mortality, and $<9.0\text{cc/kg/min}$ predicting 90-day mortality.^{16,17,18,19,20,21} In elective abdominal aortic aneurysm (AAA) repair, increased 30- and 90-day mortality was associated with $VE/VCO_2 > 42$.^{22,23,24,25} In elective colorectal surgery, early anaerobic threshold ($<11\text{cc/kg/min}$) and low $VO_{2\text{peak}}$ ($<10.6\text{cc/kg/min}$) were both associated with increased 30-day, 90-day and 2-year mortality, as well as increased postoperative length of stay.^{26,27,28} In pancreatic surgery, the predictive value of early anaerobic threshold was not as strong, but similar to AAA surgery an increased VE/VCO_2 portended an increased mortality.^{29,30,31} In studies of other surgical procedures (e.g. upper gastrointestinal, renal transplant, bariatric surgery), the data supporting CPET's prognostic ability for operative risk is not as strong – potentially resulting from lesser inherent operative risk and population differences to the other major surgeries discussed above (i.e. the patients undergoing these procedures may be younger and with less medical comorbidity).¹⁴

While many small studies have found associations between CPET results and operative complications and mortality, the largest study to date evaluating CPET as a preoperative risk assessment tool, the METS study (Measurement of Exercise Tolerance before Surgery), shows more nuanced results beyond mortality prediction alone. The METS study was a multicenter prospective cohort study evaluating 1,401 patients undergoing non-cardiac surgery. Patients with low $VO_{2\text{peak}}$ and earlier anaerobic threshold had increased post-operative complications, including surgical site infections, respiratory failure, ICU length of stay and need for re-operation. Notably, this was in the absence of an increase in postoperative cardiac events.³²

LUNG RESECTION

Pulmonary function testing performs well in identifying those at low risk for postoperative complications from anatomic lung resection (e.g. lobectomy). However, for those with marginal lung function, the use of CPET in the preoperative evaluation is suggested to help determine appropriate patients for surgery.^{33,34} Multiple studies have demonstrated that postoperative mortality was best predicted by $VO_{2\text{peak}}$.³⁵ For example, in one cohort, those with $VO_{2\text{peak}} > 20\text{cc/kg/min}$ had no post-resection deaths, and those with $VO_{2\text{peak}} < 10\text{cc/kg/min}$ had highest rates of death (29%) and complications (43%).³⁶ In another small cohort,

those with $VO_{2\text{peak}} > 15\text{cc/kg/min}$ but $FEV1 < 33\%$ had no fatalities after resection, supporting the use of CPET in those with otherwise prohibitively low $FEV1$.³⁷

LUNG VOLUME REDUCTION SURGERY

Lung volume reduction surgery (LVRS) has been shown to be effective in upper lobe predominant emphysema patients. In carefully selected patients, LVRS may improve mortality, quality of life, and exercise capacity.³⁸ In the National Emphysema Treatment Trial, over 1,000 patients were randomized to LVRS or maximum medical therapy. CPET was used to identify those who may benefit most from resection, and found that impaired peak work rate was the best predictor of who would have the most clinical benefit³⁹ (cut-off $<25\text{ W}$ in women and $<40\text{ W}$ in men). In follow-up studies after surgery, those who undergo LVRS have been shown to have improvements in $VO_{2\text{peak}}$, work-load achieved, and VE/VCO_2 .⁴⁰

PULMONARY DISEASE

Asthma

An obvious utility of CPET is the identification of exercise-induced bronchoconstriction. While a specific protocol can be used (rapid increase to 90% of peak predicted HR for 6 minutes while breathing dry air⁴¹), usually patients are being evaluated as part of a general dyspnea work-up. As such, evaluating for declines in serial post-exercise spirometries at multiple intervals can be helpful in this determination. CPET can also determine other etiologies of exercise intolerance that are common in asthma and not related to bronchospasm. Asthmatic patients can develop steroid myopathies, deconditioning and primary hyperventilation, all of which can influence exercise tolerance.⁴² Identification of non-bronchospastic causes of dyspnea may serve to limit further steroids and step-ups in therapy.⁴³ Similar to other cardio-pulmonary conditions, CPET can be used to assess objective responses to therapy, such as an increase in $VO_{2\text{peak}}$ and reduction in dynamic hyperinflation with exercise.⁴⁴

Cystic fibrosis (CF)

Cardiopulmonary exercise testing can provide valuable prognostic information in CF. One longitudinal study of CF patients over an 8-year period found that $VO_{2\text{peak}}$ correlated well with overall survival. When stratified into tertiles based on pulmonary function, the 8-year survival was 83%, 51%, and 28% from highest to lowest functional group, respectively.⁴⁵

Chronic Obstructive Pulmonary Disease (COPD)

Patients with COPD often possess multiple other comorbid conditions that can affect exercise tolerance (e.g. coronary disease, heart failure, pulmonary hypertension, anemia,

depression) and it can be difficult to ascertain which etiology one should focus additional therapy.⁴⁶ CPET may be able to discriminate the factor most responsible for exercise intolerance and enable the clinician to better direct therapy and guidance to their patient.⁴⁷ For example, in COPD patients with similar $FEV1$, CPET was shown to have the ability to detect COPD-CHF overlap, suggested by an elevated VE/VCO_2 slope and nadir, as well as a decreased end-tidal CO_2 .⁴⁸

CPET may also provide a non-invasive early measure of World Health Organization group 3 pulmonary hypertension (PH), a type of pulmonary hypertension due to primary lung pathology. In a retrospective analysis of COPD patients with available right heart catheterization and CPET data, a more significantly elevated VE/VCO_2 slope and VE/VCO_2 nadir suggested co-morbid PH in those with COPD compared to those with COPD alone, and exertional hypoxemia was more common in those with PH.⁴⁹ In another study of outpatient COPD patients without a diagnosis of CHF, exertional hypoxemia and elevated VE/VCO_2 were significantly associated with a later finding of PH.⁵⁰

However, in practice, there can be a large overlap in CPET findings between those with COPD alone and COPD associated with comorbidities, and as such it is recommended that CPET utilization should be determined on a case-by-case basis for COPD patients with dyspnea.⁵¹

Pulmonary Hypertension

While hemodynamic studies generally define the etiology of PH, certain patterns on CPET may prove helpful when uncertainty exists. Pulmonary hypertension due to left heart disease (group 2 PH) is common but it can occasionally be difficult to discriminate from pulmonary arterial hypertension (PAH; group 1 PH). On CPET, it has been demonstrated that patients with PAH have higher VE/VCO_2 slope and lower end-tidal CO_2 than those with PH due to left ventricular (LV) dysfunction.⁵² Additionally, patients with PAH are more likely to develop exertional hypoxemia during CPET than those with LV failure and those with LV failure may also exhibit a unique pattern of oscillatory ventilation during exercise that will not be present in PAH patients.⁵³

Prognosis in patients with PAH and chronic thromboembolic PH (CTEPH) is associated with CPET parameters. In a study of 86 patients with group 1 PH, peak BP below 120mmHg at maximal exercise and $VO_{2\text{peak}} < 10.4\text{cc/kg/min}$ were associated with 1-year mortality. Survival was highest in those with neither parameter (97%), worse in those with both (23%), and intermediate if only one of the two applied (79%).⁵⁴ In a study of patients with PAH or CTEPH, low $VO_{2\text{peak}} (< 11.2\text{cc/kg/min})$ predicted significantly lower 1-, 3- and 4-year survival.⁵⁵ In another study conducted with PAH and CTEPH patients, a significantly elevated VE/VCO_2 slope (>60) and VE/VCO_2 nadir >55 were associated with a high risk of death at 2 years.⁵⁶

Few therapeutic trials have used CPET variables as outcome measures, instead preferring to use the submaximal 6MWT for its ease of use. However, several small studies have shown that various PAH treatments improve $VO_{2\text{peak}}$.^{57,58} Importantly, improvements following treatment in multiple CPET parameters have been shown to correlate with improvements in RV function and survival – including increases in $VO_{2\text{peak}}$, peak heart rate, and oxygen pulse (a surrogate for stroke volume).⁵⁹

Rehabilitation

Exercise training is an integral part of pulmonary and cardiac rehabilitation programs. When available, CPET can play a role in ensuring safety prior to beginning an exercise program and can determine an appropriate training intensity leading to a more personalized exercise prescription.⁶⁰ Optimal improvement in cardiopulmonary function during a rehabilitation program occurs when consistently targeting a VO_2 of 40–80% predicted VO_2 .⁶¹ In healthy adults, $VO_{2\text{reserve}}$ correlates well with heart rate reserve (i.e. amount of VO_2 or HR remaining from maximal, respectively) and an objective determination of $VO_{2\text{reserve}}$ would not be necessary to guide a rehabilitation prescription.⁶² However, in those with congestive heart failure, objective determination of $VO_{2\text{peak}}$ and $VO_{2\text{reserve}}$ need to be determined, as it has been shown that heart rate reserve and $VO_{2\text{reserve}}$ do not correlate well in this population. Objective determination of $VO_{2\text{reserve}}$ and the HR at which this occurs enables those undergoing cardiac rehabilitation to exercise at an intensity that will more reliably lead to improvement in cardiovascular fitness and achievement of rehabilitation goals.

In attempt to improve outcomes following an intervention, there is also an emerging role for “pre-habilitation” prior to major surgery. We have discussed elsewhere in this review the association between CPET performance and surgical outcomes. If a patient is able to objectively improve their cardiopulmonary fitness as evidenced by higher $VO_{2\text{peak}}$, improved anaerobic threshold, or improved ventilatory efficiency, they may be able to improve their candidacy for surgery and reduce the likelihood of postoperative complications and mortality.⁶³

CONCLUSIONS

The comprehensive physiologic information provided by cardiopulmonary exercise testing enables a clinician to gain unique insights into the factors limiting a given patient's maximal exercise and fitness. It is invaluable and most commonly utilized in the assessment of dyspnea, but also holds prognostic information in the longitudinal assessment of cardiac and pulmonary pathologies, as well as guidance regarding appropriateness for a given surgery and risks of postoperative complications. Despite the wide breadth of physiologic information gleaned from this testing, it remains under-utilized and should be considered more often in the care of our patients.

References

1. Killian KJ, Leblanc P, Martin DH, Summers E, Jones NL, Campbell EJ. Exercise capacity and ventilatory, circulatory, and symptom limitation in patients with chronic airflow limitation. *Am Rev Respir Dis* 1992;146:935–940.
2. Albouaini K, Egred M, Alahmar A, Wright DJ. Cardiopulmonary exercise testing and its application. *Postgrad Med J*. 2007;83(985):675–682.
3. Martinez FJ, Stanopoulos I, Acero R, Becker FS, Pickering R, Beamis JF. Graded comprehensive cardiopulmonary exercise testing in the evaluation of dyspnea unexplained by routine evaluation. *Chest*. 1994 Jan;105(1):168–74.
4. American Thoracic Society; American College of Chest Physicians. ATS/ACCP Statement on cardiopulmonary exercise testing. *Am J Respir Crit Care Med*. 2003 Jan 15;167(2):211–77.
5. Smith DD. Pulmonary impairment/disability evaluation: controversies and criticisms. *Clin Pulm Med* 1995;2:334–343.
6. Mancini D, Eisen H, Kusssmaul W. Value of peak exercise oxygen consumption for optimal timing of cardiac transplantation in ambulatory patients with heart failure. *Circulation*. 1991;83:778–786
7. Stevenson LW, Steimle AE, Fonarow G, Kermani M, Kermani D, Hamilton MA, Moriguchi JD, Walden J, Tillisch JH, Drinkwater DC, et al. Improvement in exercise capacity of candidates awaiting heart transplantation. *J Am Coll Cardiol*. 1995 Jan;25(1):163–70.
8. Luiz E. Ritt, Jonathan Myers, Ricardo Stein, Ross Arena, Marco Guazzi, Paul Chase, Daniel Bensimhon, Euan Ashley, Lawrence P. Cahalin, Daniel E. Forman, Additive prognostic value of a cardiopulmonary exercise test score in patients with heart failure and intermediate risk, *International Journal of Cardiology*, Volume 178, 2015, Pages 262–264
9. O'Connor CM, Whellan DJ, Lee KL, Keteyian SJ, Cooper LS, Ellis SJ, Leifer ES, Kraus WE, Kitzman DW, Blumenthal JA, Rendall DS, Miller NH, Fleg JL, Schulman KA, McKelvie RS, Zannad F, Piña IL; HF-ACTION Investigators. Efficacy and safety of exercise training in patients with chronic heart failure: HF-ACTION randomized controlled trial. *JAMA*. 2009 Apr 8;301(14):1439–50
10. McKelvie RS. Exercise training in patients with heart failure: clinical outcomes, safety, and indications. *Heart Fail Rev*. 2008;13(1):3–1117960476
11. Belardinelli R, Georgiou D, Cianci G, Purcaro A. Randomized, controlled trial of long-term moderate exercise training in chronic heart failure: effects on functional capacity, quality of life, and clinical outcome. *Circulation*. 1999;99(9):1173–1182
12. Brunelli A, Belardinelli R, Refai M, Salati M, Socci L, Pompili C, et al. Peak oxygen consumption during cardiopulmonary exercise test improves risk stratification in candidates to major lung resection. *Chest*. 2009;135(5):1260–7.
13. Snowden CP, Prentis J, Jacques B, Anderson H, Manas D, Jones D, et al. Cardiorespiratory fitness predicts mortality and hospital length of stay after major elective surgery in older people. *Ann Surg*. 2013;257(6):999–1004.
14. Carlisle J, Swart M. Mid-term survival after abdominal aortic aneurysm surgery predicted by cardiopulmonary exercise testing. *Br J Surg*. 2007;94(8):966–9.
15. Moran J, Wilson F, Guinan E, McCormick P, Hussey J, Moriarty J. Role of cardiopulmonary exercise testing as a risk-assessment method in patients undergoing intra-abdominal surgery: a systematic review. *Br J Anaesth*. 2016 Feb;116(2):177–91.
16. Prentis JM, Manas DM, Trenell MI, Hudson M, Jones DJ, Snowden CP. Submaximal cardiopulmonary exercise testing predicts 90-day survival after liver transplantation. *Liver Transpl* 2012; 18: 152–9 14.
17. Junejo MA, Mason JM, Sheen AJ, et al. Cardiopulmonary exercise testing for preoperative risk assessment before hepatic resection. *Br J Surg* 2012; 99: 1097–104 13.

18. Bernal W, Martin-Mateos R, Lipcsey M, et al. Aerobic capacity during cardiopulmonary exercise testing and survival with and without liver transplantation for patients with chronic liver disease. *Liver Transpl* 2014; 20: 54–62
19. Kaibori M, Ishizaki M, Matsui K, et al. Assessment of preoperative exercise capacity in hepatocellular carcinoma patients with chronic liver injury undergoing hepatectomy. *BMC Gastroenterol* 2013; 13: 119
20. Nevriere R, Edme JL, Montaigne D, Boleslawski E, Pruvot FR, Dharancy S. Prognostic implications of preoperative aerobic capacity and exercise oscillatory ventilation after liver transplantation. *Am J Transplant* 2014; 14: 88–95 17.
21. Epstein SK, Freeman RB, Khayat A, Unterborn JN, Pratt DS, Kaplan MM. Aerobic capacity is associated with 100-day outcome after hepatic transplantation. *Liver Transpl* 2004; 10: 418–24
22. Grant SW, Hickey GL, Wisely NA, et al. Cardiopulmonary exercise testing and survival after elective abdominal aortic aneurysm repair. *Br J Anaesth* 2015; 114: 430–6 21.
23. Nugent AM, Riley M, Megarry J, O'Reilly MJG, MacMahon J, Lowry R. Cardiopulmonary exercise testing in the preoperative assessment of patients for repair of abdominal aortic aneurysm. *Irish J Med Sci* 1998; 167: 238–41 20.
24. Carlisle J, Swart M. Mid-term survival after abdominal aortic aneurysm surgery predicted by cardiopulmonary exercise testing. *Br J Surg* 2007; 94: 966–9
25. Hartley RA, Pichel AC, Grant SW, et al. Preoperative cardiopulmonary exercise testing and risk of early mortality following abdominal aortic aneurysm repair. *Br J Surg* 2012; 99: 1539–46 22.
26. West MA, Parry MG, Lythgoe D, et al. Cardiopulmonary exercise testing for the prediction of morbidity risk after rectal cancer surgery. *Br J Surg* 2014; 101: 1166–72
27. West MA, Asher R, Browning M, Minto G, Swart M, Richardson K, McGarrity L, Jack S, Grocott MP; Perioperative Exercise Testing and Training Society. Validation of preoperative cardiopulmonary exercise testing-derived variables to predict in-hospital morbidity after major colorectal surgery. *Br J Surg*. 2016 May;103(6):744-752
28. Lai CW, Minto G, Challand CP, et al. Patients' inability to perform a preoperative cardiopulmonary exercise test or demonstrate an anaerobic threshold is associated with inferior outcomes after major colorectal surgery. *Br J Anaesth* 2013; 111: 607–11 25.
29. Chandrabalan VV, McMillan DC, Carter R, et al. Pre-operative cardiopulmonary exercise testing predicts adverse postoperative events and non-progression to adjuvant therapy after major pancreatic surgery. *HPB (Oxford)* 2013; 15: 899–907
30. Ausania F, Vallance AE, Manas DM, et al. Double bypass for inoperable pancreatic malignancy at laparotomy: postoperative complications and long-term outcome. *Ann R Coll Surg Eng* 2012; 94: 563–8

References 31–63

Authors

Evan J. Smith, MD, Division of Pulmonary, Critical Care, and Sleep Medicine, Rhode Island Hospital and The Miriam Hospital; Providence VA Medical Center; Alpert Medical School of Brown University.

Eric J. Gartman, MD, Director of Pulmonary Function Testing Laboratory, Director of Cardiopulmonary Exercise Testing Laboratory, Providence VA Medical Center; Associate Professor of Medicine, Alpert Medical School of Brown University.

Disclosure

The views expressed in this article are those of the authors and do not necessarily reflect the position or policy of the Department of Veterans Affairs or the United States government.

Correspondence

Eric_gartman@brown.edu

The Clinical Utility of Cardiopulmonary Exercise Testing

EVAN J. SMITH, MD; ERIC J. GARTMAN, MD

31. Ausania F, Snowden CP, Prentis JM, et al. Effects of low cardiopulmonary reserve on pancreatic leak following pancreaticoduodenectomy. *Br J Surg* 2012; 99: 1290–4 29.
32. Wijeyesundera DN, Pearse RM, Shulman MA, Abbott TEF, Torres E, Ambosta A, Croal BL, Granton JT, Thorpe KE, Grocott MPW, Farrington C, Myles PS, Cuthbertson BH; METS study investigators. Assessment of functional capacity before major non-cardiac surgery: an international, prospective cohort study. *Lancet*. 2018 Jun 30;391(10140):2631-2640.
33. Brunelli A, Kim AW, Berger KI, Addrizzo-Harris DJ. Physiologic evaluation of the patient with lung cancer being considered for resectional surgery: Diagnosis and management of lung cancer, 3rd ed: American College of Chest Physicians evidence-based clinical practice guidelines. *Chest*. 2013 May;143(5 Suppl):e166S-e190S.
34. Brunelli A, Charloux A, Bolliger CT, Rocco G, Sculier JP, Varela G, Licker M, Ferguson MK, Faivre-Finn C, Huber RM, Clini EM, Win T, De Ruysscher D, Goldman L; European Respiratory Society and European Society of Thoracic Surgeons joint task force on fitness for radical therapy. ERS/ESTS clinical guidelines on fitness for radical therapy in lung cancer patients (surgery and chemo-radiotherapy). *Eur Respir J*. 2009 Jul;34(1):17-41.
35. Brutsche MH, Spiliopoulos A, Bolliger CT, et al. Exercise capacity and extent of resection as predictors of surgical risk in lung cancer. *Eur Respir J*, 15 (2000), pp. 828-832
36. Bechara B, Wetstein L. Assessment of Exercise Oxygen Consumption as Preoperative Criterion for Lung Resection, *The Annals of Thoracic Surgery*, Volume 44, Issue 4, 1987, Pages 344-349
37. Wyser C, Stulz P, Soler M, Tamm M, Muller-Brand J, Habicht J, Perruchoud AP, Bolliger CT. Prospective evaluation of an algorithm for the functional assessment of lung resection candidates. *Am J Respir Crit Care Med* 1999;159:1450-1456.
38. Marchetti, N., & Criner, G. J. Surgical approaches to treating emphysema: Lung volume reduction surgery, bullectomy, and lung transplantation. *Seminars in Respiratory and Critical Care Medicine*, 2015 36, 592–608
39. Ramsey, S. D., Berry, K., Etzioni, R., Kaplan, R. M., Sullivan, S. D., & Wood, D. E. (2003). National Emphysema Treatment Trial Research Group. Cost effectiveness of lung volume reduction surgery for patients with severe emphysema. *New England Journal of Medicine*, 348, 2092–2102.
40. Hilary F Armstrong, Nicole E Dussault, Wilawan Thirapatapong, Renee S Lemieux, Byron M Thomashow and Matthew N Bartels. Ventilatory Efficiency Before and After Lung Volume Reduction Surgery, *Respiratory Care* January 2015, 60 (1) 63-71
41. T. Stensrud, S. Berntsen, K.-H. Carlsen Humidity influences exercise capacity in subjects with exercise-induced bronchoconstriction (EIB) *Respir. Med.*, 100 (9) (2006), pp. 1633-1641
42. Boutou AK, Daniil Z, Pitsiou G, Papakosta D, Kioumis I, Stanopoulos I. Cardiopulmonary exercise testing in patients with asthma: What is its clinical value? *Respir Med*. 2020 Jun;167:105953.
43. McNicholl DM, Megarry J, McGarvey LP, Riley MS, Heaney LG. The utility of cardiopulmonary exercise testing in difficult asthma. *CHEST*. 2011;139(5):1117-1123.
44. Schäper C, Gläser S, Felix SB, et al. Omalizumab treatment and exercise capacity in severe asthmatics – results from a pilot study. *Respir Med*. 2011;105(1):3-7.
45. Nixon PA, Orenstein DM, Kelsey SF, Doershuk CF. The prognostic value of exercise testing in patients with cystic fibrosis. *N Engl J Med* 1992;327:1785-1788.
46. Divo M, Cote C, de Torres JP, Casanova C, Marin JM, Pinto-Plata V, Zulueta J, Cabrera C, Zagaceta J, Hunninghake G, Celli B, BODE Collaborative Group. Comorbidities and risk of mortality in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med*. 2012 Jul 15;186(2):155-61
47. Boutou AK, Zafeiridis A, Pitsiou G, Dipla K, Kioumis I, Stanopoulos I. Cardiopulmonary exercise testing in chronic obstructive pulmonary disease: An update on its clinical value and applications. *Clin Physiol Funct Imaging*. 2020 Jul;40(4):197-206
48. Apostolo A, Laveneziana P, Palange P, Agalbatto C, Molle R, Popovic D, Bussotti M, Internullo M, Sciomer S, Bonini M, Alencar MC, Godinas L, Arbex F, Garcia G, Neder JA, Agostoni P. Impact of chronic obstructive pulmonary disease on exercise ventilatory efficiency in heart failure. *Int J Cardiol*. 2015;189:134-40.
49. Holverda S, Bogaard H, J, Groepenhoff H, Postmus P, E, Boonstra A, Vonk-Noordegraaf A. Cardiopulmonary Exercise Test Characteristics in Patients with Chronic Obstructive Pulmonary Disease and Associated Pulmonary Hypertension. *Respiration* 2008;76:160-167
50. Skjørten, I., Hilde, J. M., Melsom, M. N., Hisdal, J., Hansteen, V., Steine, K., & Humerfelt, S. (2017). Cardiopulmonary exercise test and PaO2 in evaluation of pulmonary hypertension in COPD. *International Journal of Chronic Obstructive Pulmonary Disease*, 13, 91–100
51. Neder J. A., Berton D. C., Rocha A., Arbex F. F., Alencar M. C. N., Degani-Costa L. H., et al. (2018). "Abnormal patterns of response to incremental CPET," in *Clinical Exercise Testing*, eds Palange P., Laveneziana P., Neder J. A., Ward S. A. (Lausanne: European Respiratory Society;),
52. Deboeck G, Niset G, Lamotte M, Vachiéry JL, Naeije R. Exercise testing in pulmonary arterial hypertension and in chronic heart failure. *Eur Respir J* 2004;23:747-751
53. Liu WH, Luo Q, Liu ZH, Zhao Q, Xi QY, Zhao ZH. Differences in pulmonary function and exercise capacity in patients with idiopathic dilated cardiomyopathy and idiopathic pulmonary arterial hypertension. *Heart Lung* 2014;43:317-321.
54. Wensel R, Opitz CF, Anker SD, Winkler J, Höffken G, Kleber FX, Sharma R, Hummel M, Hetzer R, Ewert R. Assessment of survival in patients with primary pulmonary hypertension: importance of cardiopulmonary exercise testing. *Circulation* 2002;106:319-324.
55. Grünig E, Tiede H, Enyimayew EO, Ehlken N, Seyfarth HJ, Bossone E, D'Andrea A, Naeije R, Olschewski H, Ulrich S, Nagel C, Halank M, Fischer C. Assessment and prognostic relevance of right ventricular contractile reserve in patients with severe pulmonary hypertension. *Circulation*. 2013 Oct 29;128(18):2005-15
56. Schwaiblmair M, Faul C, von Scheidt W, Berghaus TM. Ventilatory efficiency testing as prognostic value in patients with pulmonary hypertension. *BMC Pulm Med* 2012;12:23
57. Wax D, Garofano R, Barst RJ. Effects of long-term infusion of prostacyclin on exercise performance in patients with primary pulmonary hypertension. *Chest* 1999;116:914-920.
58. Oudiz RJ, Roveran G, Hansen JE, Sun X-G, Wasserman K. Effect of sildenafil on ventilatory efficiency and exercise tolerance in pulmonary hypertension. *Eur J Heart Fail* 2007;9:917-921
59. Groepenhoff H, Vonk-Noordegraaf A, van de Veerdonk MC, Boonstra A, Westerhof N, Bogaard HJ. Prognostic relevance of changes in exercise test variables in pulmonary arterial hypertension. *Plos One* 2013
60. Casaburi R, Patessio A, Ioli F, Zanaboni S, Donner CF, Wasserman K. Reductions in exercise lactic acidosis and ventilation as a result of exercise training in patients with obstructive lung disease. *Am Rev Respir Dis* 1991;143:9-18
61. Mezzani A, Corra` U, Giordano A, Cafagna M, Adriano EP, Giannuzzi P. Unreliability of the % VO2 reserve versus % heart rate reserve relationship for aerobic effort relative intensity assessment in chronic heart failure patients on or off-beta-blocking therapy. *Eur J Cardiovasc Prev Rehabil* 2007; 14:92-98.
62. Tabet JY, Metra M, Thabut G, Logeart D, Cohen-Solal A. Prognostic value of cardiopulmonary exercise variables in chronic heart failure patients with or without beta-blocker therapy. *Am J Cardiol* 2005; 98:500-503
63. Hughes, M.J., Hackney, R.J., Lamb, P.J. et al. Prehabilitation Before Major Abdominal Surgery: A Systematic Review and Meta-analysis. *World J Surg* 43, 1661–1668 (2019).

Updates on the Management of Cystic Fibrosis: Development of Modulators and Advancement of Antibiotic Therapies

CHELSEA BOYD, MD; ROGER D. AUTH, MD; MICHAEL BLUNDIN, MD; DEBASREE BANERJEE, MD, MS

KEYWORDS: cystic fibrosis, CFTR, modulator therapy, suppressive antibiotics

INTRODUCTION

Cystic fibrosis (CF) is a rare autosomal recessive, multi-organ disease that affects over seventy thousand people worldwide. While CF is the most common heritable disease in Caucasians, improvements in newborn screening and wider availability of genetic testing have shed light on the increasing incidence in non-Caucasian individuals.¹ In decades past, CF was a disease of childhood that was often fatal before adulthood. However, utilization of dedicated multidisciplinary care centers and advances in therapeutics have led to dramatic improvements in lifespan and quality of life. The median life expectancy for persons with cystic fibrosis (PwCF) is now approaching fifty years in many countries.¹

CF was first characterized in 1938 after the discovery of pancreatic fibrosis in individuals with steatorrhea and nutritional deficiencies previously attributed to celiac disease.² Several decades later the discovery of increased sweat salinity in this population led to the development of the preferred diagnostic study, the sweat chloride test.^{3,4} While CF was believed to be caused by a recessive genetic defect as early as the 1940s, the cystic fibrosis transmembrane regulator (CFTR) gene was not discovered until 1989.^{5,6} The genetic hallmark of CF is absent or impaired function of the CFTR protein and over 2,000 pathogenic variants of the CFTR gene have been described.⁷ The most common pathogenic mutation is the deletion of phenylalanine in position 508 (F508del), which results in misfolding of the CFTR protein.⁸

CFTR is present on epithelial membranes in the lungs, gastrointestinal tract, and exocrine pancreas, and is responsible for the chloride transport vital to normal mucus production, function, and clearance. CFTR also has an important role in bicarbonate transport and regulation of the epithelial sodium channel (ENaC), two major determinants of mucosal pH and fluid movement across the cellular membrane. In PwCF, decreased or absent CFTR leads to thick mucus, impaired ciliary function, and altered mucosal pH, ultimately resulting in decreased ability to clear respiratory secretions, recurrent respiratory infections and inflammation, nutrient malabsorption, and exocrine pancreas

dysfunction. Research has also demonstrated direct and indirect effects of the dysfunctional CFTR protein on the innate and adaptive immune systems, further predisposing to recurrent lung infections, bronchiectasis, and reduced lung function. These injuries ultimately lead to respiratory failure, the major cause of mortality in PwCF.

The last decade has brought tremendous progress to the treatment of CF. Novel therapeutics, particularly medications designed to improve the production of functional CFTR, collectively termed modulators, have the capacity to improve lung function, decrease pulmonary infections, and improve quality of life. This article will review the development and validation of modulator therapies, as well as discuss updates on the state of antibiotic therapies, two mainstays of modern CF care.

NOVEL THERAPEUTICS: MODULATORS

Production of functional CFTR protein is a multistep process that includes transcription of deoxyribonucleic acid (DNA) into messenger ribonucleic acid (mRNA), translation into a sequence of amino acids, processing to fold and transport the resultant protein to the cell membrane and maintaining proper gating and stability to allow sufficient ion conductance. Mutations in the CFTR gene that prevent any of these processes from occurring correctly can result in functional protein deficiency and serve as potential therapeutic targets. CFTR mutations are classified into six categories based on their primary downstream effect, though one mutation may cause defects in multiple classes.

Class I, II, and III mutations involve premature termination codons, protein processing mutations, and gating mutations, respectively, leading to minimal or no CFTR activity and severe clinical phenotypes. These mutations are classified as minimal function (MF) mutations and are often not amenable to targeted therapies. Class IV mutations affect ion conductance, class V mutations blunt CFTR protein production, and class VI mutations cause instability at the cell surface. Class IV, V, and VI mutations are classified as residual function (RF) mutations because some functional CFTR is formed, typically generating less severe clinical phenotypes.⁹ These mutations have become some of the first therapeutic targets for modulator therapies (**Figures 1 and 2**).

Figure 1. CFTR Mutation Classification

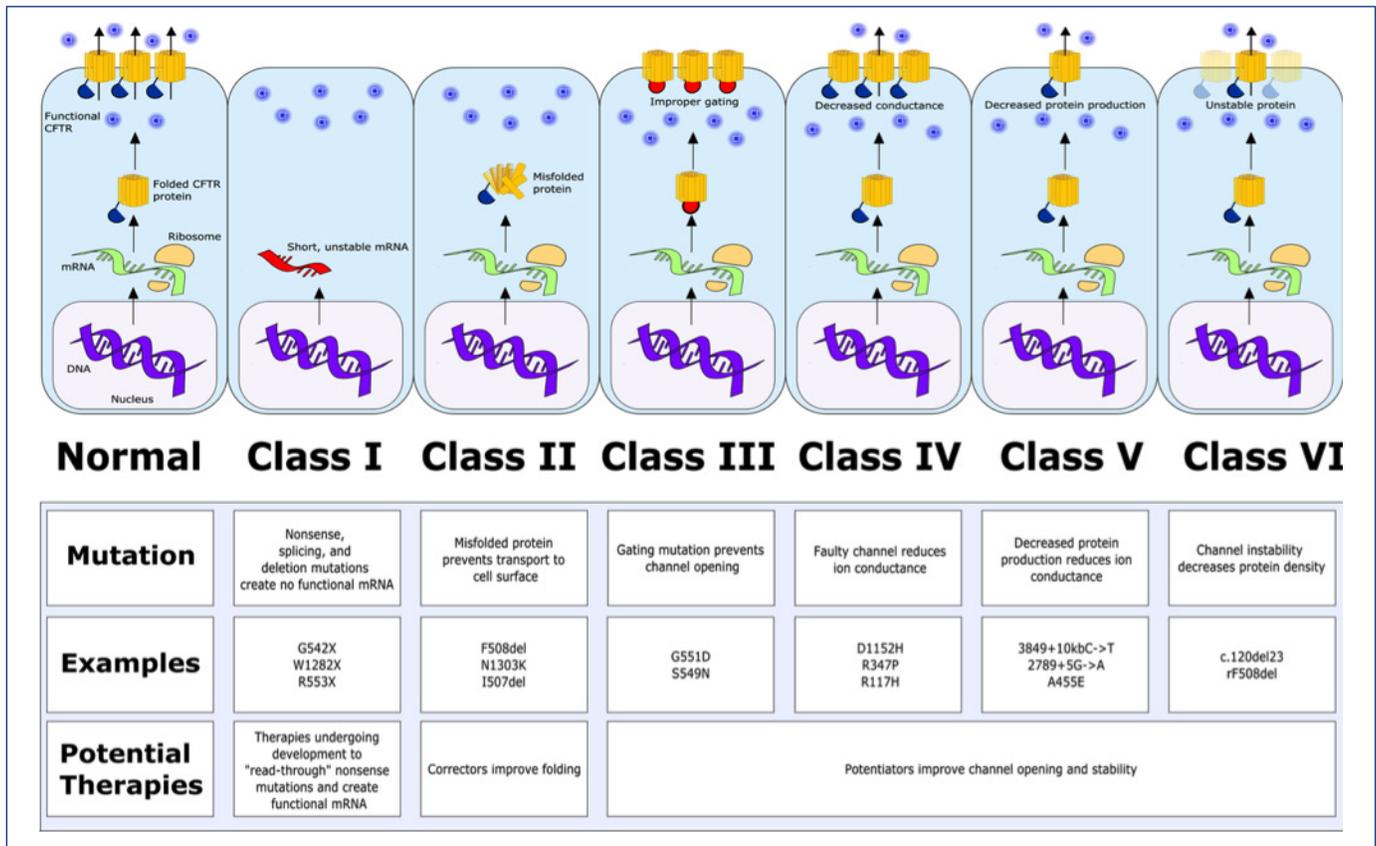
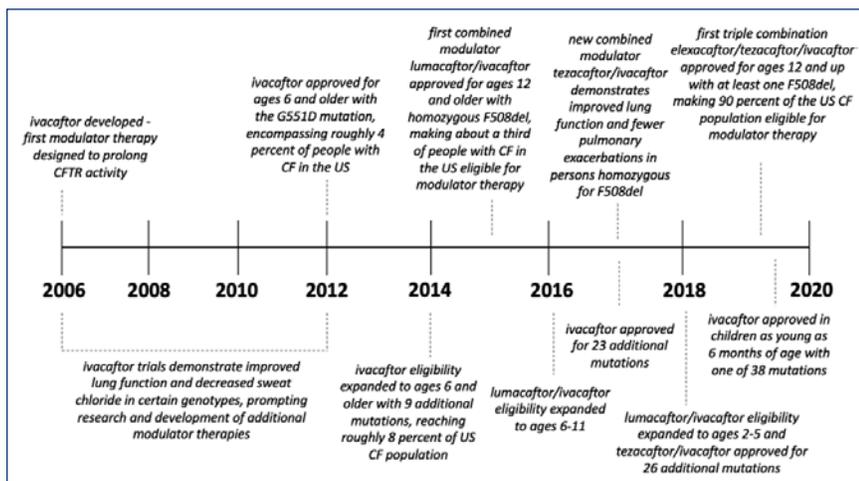


Figure 2. Timeline of Modulator Therapy Development and Approval



Ivacaftor

In 2006, ivacaftor (Kalydeco®) was developed and became the first modulator to enter clinical trials. Ivacaftor acts on CFTR gating, prolonging the duration of CFTR opening. This type of therapy is known as a “potentiator,” because it prolongs the activity of CFTR already present at the cell surface. In 2007, a pilot clinical trial demonstrated significant

improvement in clinical outcomes with ivacaftor including an 8.7 percent increase in percent predicted forced expiratory volume in one second (ppFEV1) and median decrease in sweat chloride by -59.5 mmol/L.¹⁰ Ivacaftor became available in the United States (US) in 2012 for patients six years and older with one specific CF mutation (G551D). Despite the drug’s limited eligibility, this landmark discovery demonstrated clinically meaningful improvements in lung function and laid the groundwork for future study. Additionally, a recent observational study that followed US patients starting ivacaftor within the first years of commercial availability provided evidence that the benefits of ivacaftor extend well beyond improved lung function. This study demonstrated that in the subsequent three years, patients taking ivacaftor experienced significantly lower risk of death, transplantation, hospitalization, pulmonary exacerbations, CF-related diabetes, bone or joint complications, and cultures involving methicillin-resistant *Staphylococcus aureus* (MRSA), *Pseudomonas aeruginosa*, and *Aspergillus* species.¹¹

Throughout the decade following its initial approval, the FDA progressively expanded approval for ivacaftor to ultimately include patients four months of age and older with 38 RF mutations.⁹ Still, by 2014 only approximately eight percent of the US CF population qualified for ivacaftor based on their mutations.

Lumacaftor

The next modulator to be developed was lumacaftor, the first member of a class of “correctors.” Correctors are named for their ability to restore the shape of poorly processed CFTR protein, thereby improving successful transit to and activity in the cell membrane. Although *in vitro* studies suggested that lumacaftor increases the density of functional CFTR at the cell surface, phase II clinical trials in patients with homozygous F508del mutations were only able to demonstrate a dose-dependent decrease in sweat chloride levels. There was no improvement in clinically relevant endpoints such as lung function or patient-reported outcomes.¹² However, when combined with the potentiator ivacaftor, the combination lumacaftor/ivacaftor (known as Orkambi[®]) was shown in phase II and III clinical trials to improve ppFEV1 by 2.6–4.0 percentage points, decrease pulmonary exacerbations by 30–39 percent, and decrease events leading to hospitalization and use of intravenous antibiotics when compared with placebo.^{13,14} As a result, in 2015 the FDA approved lumacaftor/ivacaftor for patients ages 12 and older who are homozygous for the F508del mutation, expanding availability of modulator therapy to approximately one third of US PwCF. Subsequently, studies demonstrated reduced pulmonary exacerbations to approximately 0.6 exacerbations per patient per year with lumacaftor/ivacaftor when compared with placebo.¹⁵ Another study demonstrated sustained benefit in slowing ppFEV1 decline over an extended study period of 96 weeks, and two additional clinical trials redemonstrated efficacy and safety in younger populations.^{16–18} Together, trials supporting lumacaftor/ivacaftor led to FDA approval for patients aged two and older by 2018.

Tezacaftor

In 2017, another corrector called tezacaftor was developed, with a similar structure to lumacaftor but improved pharmacokinetics and fewer respiratory side effects.⁹ It was tested alone in phase II clinical trials and in combination with ivacaftor in phase II and III trials, both in patients homozygous for F508del and in patients with one F508del mutation and another RF mutation. Phase II clinical trials demonstrated decreased sweat chloride levels in higher-dose tezacaftor and in most tezacaftor/ivacaftor groups compared with placebo, but increased ppFEV1 only in tezacaftor/ivacaftor combination groups.¹⁹ Combination tezacaftor/ivacaftor (Symdeko[®]) was found to increase ppFEV1 in patients homozygous and heterozygous for F508del with an additional RF mutation.^{19,20} Phase III clinical trials demonstrated four percent

absolute increase in ppFEV1 and 35 percent decrease in pulmonary exacerbations with tezacaftor/ivacaftor compared to placebo.²¹ In 2018, the FDA approved tezacaftor/ivacaftor for patients 12 years and older homozygous for F508del or heterozygous F508del with a second RF mutation. This again markedly increased the pool of PwCF eligible for modulator therapy. Following publication of a phase III clinical trial that demonstrated a similar safety profile with tezacaftor/ivacaftor in patients ages six through 11, FDA approval was extended to this age group in 2019.²²

Elexacaftor

Nearly a decade after the introduction of ivacaftor, new modulators and combinations were undergoing development and preclinical trials. Although major advancements had been made, improvements in lung function with available modulator treatments remained limited and there were minimal options for patients with certain mutations, particularly MF mutations.⁹ However, 2019 proved to be another landmark year for the CF community when a triple therapy containing two correctors, elexacaftor and tezacaftor, and potentiator ivacaftor was released for patients 12 years and older with at least one F508del mutation. This extended availability of modulator therapy to nearly 90 percent of PwCF. Further, phase III clinical trials demonstrated marked improvement with 41.8mmol/L decrease in sweat chloride, 14.3 percent increase in ppFEV1 over 24 weeks, 63.0 percent decrease in pulmonary exacerbations, and a 20.2 point increase in the Cystic-Fibrosis Questionnaire-Revised score indicating improved quality of life with elexacaftor/tezacaftor/ivacaftor (Trikafta[®]) compared with placebo.²³ Studies are underway evaluating the safety and efficacy of elexacaftor/tezacaftor/ivacaftor long-term and in younger populations. Additionally, an ongoing observational study entitled PROMISE aims to assess for broader systemic improvements with triple therapy.

There are several treatments designed to restore CFTR function that are currently undergoing phase II clinical trials including correctors, potentiators, and a compound designed to target premature termination mutations. Others are currently in phase I clinical trials, including a potentiator and an inhaled therapy designed to deliver CFTR mRNA to the lungs.

UPDATES ON ANTIBIOTIC THERAPIES

PwCF are chronically colonized with bacteria that alter the lung microbiome.²⁴ Common pathogens include *Staph aureus* and *Hemophilus influenzae* in early disease with progression to resistant organisms that can form biofilms such as *Pseudomonas aeruginosa* and *Burkholderia cepacia*. Colonization with *Pseudomonas aeruginosa* and *Burkholderia cepacia* is correlated with worsening lung function and as such, suppressive therapy with inhaled antibiotics is a cornerstone of CF management.^{25,26} There is also increased susceptibility in PwCF for chronic infections with opportunistic

pathogens such as mycobacterium avium complex (MAC). There are ongoing efforts to develop alternative anti-infective therapies for chronic use, especially for the resistant and diverse pathogens now recognized to colonize the CF lung. Additionally, acute CF exacerbations are repeatedly treated with short-term oral or intravenous antibiotics. There are ongoing investigations to optimize acute antibiotic treatment to minimize exposure and toxicities.

Chronic suppression

Inhaled antibiotics are the primary treatment for chronic *Pseudomonas* infection. Inhaled tobramycin and inhaled aztreonam became available in 1997 and 2010 respectively, after studies demonstrated improved lung function, decreased *Pseudomonas* burden in sputum, improved respiratory symptom scores, and decreased risk of pulmonary exacerbations and hospitalizations with chronic therapy.²⁷⁻³¹ Inhaled antibiotics are typically cycled every 28 days to reduce selective pressure for antibiotic resistance.²⁹ It is worthwhile to note that oral azithromycin is also approved for chronic *Pseudomonas* suppression after studies demonstrated improved lung function and decreased risk of exacerbations. However, recent studies suggest oral azithromycin may decrease the efficacy of tobramycin and therefore should be used with caution.³²⁻³⁴

In 2018, inhaled liposomal amikacin became the first therapy approved under the FDA Limited Population Pathway for Antibacterial and Antifungal Drugs designed to accelerate development of medications for serious infections affecting small populations. It was approved for treatment-refractory mycobacterium avium complex in adults, although notably the primary study leading to its approval excluded PwCF.³⁵ Recent studies have also suggested inhaled amikacin liposomal suspension to be non-inferior to inhaled tobramycin for treatment of chronic *Pseudomonas*, although results of a phase III clinical trial evaluating this have not yet been published and it is not FDA-approved for this indication.³⁶

Multiple studies have evaluated the efficacy and safety of inhaled levofloxacin, including phase II clinical trials demonstrating decreased sputum *Pseudomonas* density, dose-dependent improvements in lung function, and reduced need for other inhaled or systemic antipseudomonal antibiotics compared with placebo.³⁷ However, phase III clinical trials failed to demonstrate a difference in pulmonary exacerbations between inhaled levofloxacin and placebo.³⁸ Inhaled levofloxacin is not FDA approved in the US, although it is available in the European Union and Canada.

Studies are ongoing to address the diagnosis and treatment of other pathogens that colonize the CF lung. For example, an ongoing prospective study aims to evaluate a standardized approach for diagnosis and management of nontuberculous mycobacteria. Additionally, inhaled vancomycin recently underwent phase III clinical trials for chronic MRSA, however it did not improve lung function or reduce pulmonary

exacerbations and is not currently undergoing further development.

There are also several innovative treatments designed to combat chronic infections undergoing phase II trials including intravenous gallium, bacteriophage therapy, and intravenous nitrous oxide. Gallium is thought to inhibit iron-dependent processes and may kill antibiotic-resistant *Pseudomonas*.³⁹ Bacteriophage therapy utilizes viruses targeted to kill specific bacterial sources, and has been shown to eliminate more than 80 percent of *Pseudomonas* strains in PwCF.⁴⁰ Nitrous oxide may help eliminate biofilms and nontuberculous mycobacteria.⁴¹ Many other anti-infective therapies are in phase I trials or pre-clinical development.

Acute exacerbations

Treatment with oral or intravenous antibiotics during pulmonary exacerbations has long been a pillar of CF management. However, the optimal antibiotic selection and duration for acute exacerbations remains unknown.

Due to the recurrent need for antibiotics and increasing prevalence of antibiotic resistance, standard practice for selecting antibiotics during acute CF exacerbations relies on *in vitro* antimicrobial susceptibility testing (AST). However, a 2019 systematic review demonstrated that 11 out of 13 studies evaluating AST for acute exacerbations demonstrated no relationship between AST and clinical response to treatment, calling the utility of this practice into question.⁴² As opposed to isolated monomicrobial infections in otherwise healthy patients, AST may not accurately capture the heterogeneous microbiology of the CF lung or predict clinical response to treatment and thus, may not be effective in guiding treatment decisions.

Additionally, the recurrent need for nephrotoxic and ototoxic antibiotics raises the question of minimum effective dosing regimens. A 2017 Cochrane review found once daily dosing of aminoglycosides equally as effective as three times daily dosing with no difference in lung function or time to next exacerbation requiring intravenous antibiotics. There was a lower risk of nephrotoxicity in children with once daily dosing.⁴³ Additionally, an ongoing randomized controlled trial entitled STOP2 aims to evaluate the efficacy and safety of 10-day, 14-day, and 21-day intravenous antibiotic regimens during acute exacerbations by comparing improvements in lung function and respiratory symptom scores. Altogether, it may be possible in the near future to decrease the frequency and duration of intravenous antibiotics administered during acute exacerbations, an important step in minimizing total lifetime antibiotic exposure and toxicity.

CONCLUSIONS

The development of modulator therapies that target the underlying pathophysiology of CF has revolutionized care for PwCF. Still, ongoing research and development promises

upcoming advances in both combination and novel modulator therapies as well as innovative agents for those with mutations not currently served by existing therapies. Further, optimization of both acute and chronic antibiotic treatments will provide more efficient regimens that maximize efficacy and minimize toxicity.

While substantial progress has been made, there remains ample opportunity to improve care for PwCF. Anticipating increased longevity, considerations for ongoing CF care must be prioritized to optimize quality of life. Efforts include, but are not limited to, improving screening and management of CF-related chronic illnesses as well improving opportunities for family planning. Day-to-day quality of life can be improved by working to minimize the burden of CF care. To this end, an ongoing study entitled SIMPLIFY will examine the outcomes of withdrawing adjunctive therapies for those on modulator therapy.

With recent advancements and continued efforts toward safer, more efficacious, and streamlined treatments, individuals born with CF in 2021 will enjoy quality life years well beyond that of their predecessors.

References

- Bell, S.C., et al. *The future of cystic fibrosis care: a global perspective*. The Lancet Respiratory Medicine, 2020. 8(1): p. 65-124.
- Andersen, D.H. *Cystic fibrosis of the pancreas and its relation to celiac disease: a clinical and pathologic study*. American journal of Diseases of Children, 1938. 56(2): p. 344-399.
- di Sant'Agnese, P.A., et al. *Abnormal electrolyte composition of sweat in cystic fibrosis of the pancreas: clinical significance and relationship to the disease*. Pediatrics, 1953. 12(5): p. 549-563.
- Gibson, L.E. and R.E. Cooke. *A test for concentration of electrolytes in sweat in cystic fibrosis of the pancreas utilizing pilocarpine by iontophoresis*. Pediatrics, 1959. 23(3): p. 545-549.
- Tsui, L.-C. and Dorfman R. *The cystic fibrosis gene: a molecular genetic perspective*. Cold Spring Harbor perspectives in medicine, 2013. 3(2): p. a009472.
- Rommens, J.M., et al. *Identification of the cystic fibrosis gene: chromosome walking and jumping*. Science, 1989. 245(4922): p. 1059-1065.
- Boyle, M.P. and K. De Boeck. *A new era in the treatment of cystic fibrosis: correction of the underlying CFTR defect*. The Lancet Respiratory Medicine, 2013. 1(2): p. 158-163.
- Balch, W.E., D.M. Roth, and D.M. Hutt. *Emergent properties of proteostasis in managing cystic fibrosis*. Cold Spring Harbor perspectives in biology, 2011. 3(2): p. a004499.
- Bardin, E., et al. *Modulators of CFTR. Updates on clinical development and future directions*. European journal of medicinal chemistry, 2021: p. 113195.
- Accurso, F.J., et al. *Effect of VX-770 in persons with cystic fibrosis and the G551D-CFTR mutation*. New England Journal of Medicine, 2010. 363(21): p. 1991-2003.
- Bessonova, L., et al. *Data from the US and UK cystic fibrosis registries support disease modification by CFTR modulation with ivacaftor*. Thorax, 2018. 73(8): p. 731-740.
- Clancy, J., et al. *Results of a phase IIa study of VX-809, an investigational CFTR corrector compound, in subjects with cystic fibrosis homozygous for the F508del-CFTR mutation*. Thorax, 2012. 67(1): p. 12-18.
- Boyle, M.P., et al. *A CFTR corrector (lumacaftor) and a CFTR potentiator (ivacaftor) for treatment of patients with cystic fibrosis who have a phe508del CFTR mutation: a phase 2 randomized controlled trial*. The Lancet Respiratory medicine, 2014. 2(7): p. 527-538.
- Wainwright, C.E., et al. *Lumacaftor-ivacaftor in patients with cystic fibrosis homozygous for Phe508del CFTR*. New England Journal of Medicine, 2015. 373(3): p. 220-231.
- McColley, S.A., et al. *Lumacaftor/ivacaftor reduces pulmonary exacerbations in patients irrespective of initial changes in FEV1*. Journal of Cystic Fibrosis, 2019. 18(1): p. 94-101.
- Konstan, M.W., et al. *Assessment of safety and efficacy of long-term treatment with combination lumacaftor and ivacaftor therapy in patients with cystic fibrosis homozygous for the F508del-CFTR mutation (PROGRESS): a phase 3, extension study*. The Lancet Respiratory Medicine, 2017. 5(2): p. 107-118.
- Milla, C.E., et al. *Lumacaftor/ivacaftor in patients aged 6-11 years with cystic fibrosis and homozygous for F508del-CFTR*. American journal of respiratory and critical care medicine, 2017. 195(7): p. 912-920.
- Ratjen, F., et al. *Efficacy and safety of lumacaftor and ivacaftor in patients aged 6-11 years with cystic fibrosis homozygous for F508del-CFTR: a randomised, placebo-controlled phase 3 trial*. The Lancet Respiratory medicine, 2017. 5(7): p. 557-567.
- Donaldson, S.H., et al. *Tezacaftor/ivacaftor in subjects with cystic fibrosis and F508del/F508del-CFTR or F508del/G551D-CFTR*. American journal of respiratory and critical care medicine, 2018. 197(2): p. 214-224.
- Rowe, S.M., et al. *Tezacaftor-ivacaftor in residual-function heterozygotes with cystic fibrosis*. New England Journal of Medicine, 2017. 377(21): p. 2024-2035.
- Taylor-Cousar, J.L., et al. *Tezacaftor-ivacaftor in patients with cystic fibrosis homozygous for Phe508del*. New England Journal of Medicine, 2017. 377(21): p. 2013-2023.
- Walker, S., et al. *A phase 3 study of tezacaftor in combination with ivacaftor in children aged 6 through 11 years with cystic fibrosis*. Journal of Cystic Fibrosis, 2019. 18(5): p. 708-713.
- Middleton, P.G., et al. *Elexacaftor-tezacaftor-ivacaftor for cystic fibrosis with a single Phe508del allele*. New England Journal of Medicine, 2019. 381(19): p. 1809-1819.
- Surette, M.G. *The cystic fibrosis lung microbiome*. Annals of the American Thoracic Society, 2014. 11(Supplement 1): p. S61-S65.
- Folescu, T.W., et al. *Burkholderia cepacia complex: clinical course in cystic fibrosis patients*. BMC pulmonary medicine, 2015. 15(1): p. 1-6.
- Kosorok, M.R., et al. *Acceleration of lung disease in children with cystic fibrosis after Pseudomonas aeruginosa acquisition*. Pediatric pulmonology, 2001. 32(4): p. 277-287.
- Assael, B.M., et al. *Inhaled aztreonam lysine vs. inhaled tobramycin in cystic fibrosis: a comparative efficacy trial*. Journal of Cystic fibrosis, 2013. 12(2): p. 130-140.
- McCoy, K.S., et al. *Inhaled aztreonam lysine for chronic airway Pseudomonas aeruginosa in cystic fibrosis*. American journal of respiratory and critical care medicine, 2008. 178(9): p. 921-928.
- Nichols, D.P., et al. *Developing inhaled antibiotics in cystic fibrosis: current challenges and opportunities*. Annals of the American Thoracic Society, 2019. 16(5): p. 534-539.
- Ramsey, B.W., et al. *Intermittent administration of inhaled tobramycin in patients with cystic fibrosis*. New England Journal of Medicine, 1999. 340(1): p. 23-30.
- Retsch-Bogart, G.Z., et al. *Efficacy and safety of inhaled aztreonam lysine for airway pseudomonas in cystic fibrosis*. Chest, 2009. 135(5): p. 1223-1232.
- Nick, J.A., et al. *Azithromycin may antagonize inhaled tobramycin when targeting Pseudomonas aeruginosa in cystic fibrosis*. Annals of the American Thoracic Society, 2014. 11(3): p. 342-350.
- Saiman, L., et al. *Azithromycin in patients with cystic fibrosis chronically infected with Pseudomonas aeruginosa: a randomized controlled trial*. Jama, 2003. 290(13): p. 1749-1756.

34. Nichols, D.P., et al. *Impact of azithromycin on the clinical and antimicrobial effectiveness of tobramycin in the treatment of cystic fibrosis*. Journal of Cystic Fibrosis, 2017. **16**(3): p. 358-366.
35. Griffith, D.E., et al. *Amikacin liposome inhalation suspension for treatment-refractory lung disease caused by Mycobacterium avium complex (CONVERT). A prospective, open-label, randomized study*. American journal of respiratory and critical care medicine, 2018. **198**(12): p. 1559-1569.
36. Bilton, D., et al. *Amikacin liposome inhalation suspension for chronic Pseudomonas aeruginosa infection in cystic fibrosis*. Journal of Cystic Fibrosis, 2020. **19**(2): p. 284-291.
37. Geller, D.E., et al. *Levofloxacin inhalation solution (MP-376) in patients with cystic fibrosis with Pseudomonas aeruginosa*. American journal of respiratory and critical care medicine, 2011. **183**(11): p. 1510-1516.
38. Flume, P.A., et al. *A phase 3, multi-center, multinational, randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of levofloxacin inhalation solution (APT-1026) in stable cystic fibrosis patients*. Journal of Cystic Fibrosis, 2016. **15**(4): p. 495-502.
39. Goss, C.H., et al. *Gallium disrupts bacterial iron metabolism and has therapeutic effects in mice and humans with lung infections*. Science translational medicine, 2018. **10**(460).
40. Holger, D., et al. *Clinical Pharmacology of Bacteriophage Therapy: A Focus on Multidrug-Resistant Pseudomonas aeruginosa Infections*. Antibiotics, 2021. **10**(5): p. 556.
41. Laudone, T.W., et al. *Novel therapies for treatment of resistant and refractory nontuberculous mycobacterial infections in patients with cystic fibrosis*. Pediatric Pulmonology, 2021. **56**: p. S55-S68.
42. Somayaji, R., et al. *Antimicrobial susceptibility testing (AST) and associated clinical outcomes in individuals with cystic fibrosis: a systematic review*. Journal of Cystic Fibrosis, 2019. **18**(2): p. 236-243.
43. Bhatt, J., N. Jahnke, and A.R. Smyth. *Once-daily versus multiple-daily dosing with intravenous aminoglycosides for cystic fibrosis*. Cochrane Database of Systematic Reviews, 2019(9).

Authors

Chelsea Boyd, MD, Department of Internal Medicine-Pediatrics, Alpert Medical School of Brown University, Providence, RI.
 Roger D. Auth, MD, Department of Medicine, Alpert Medical School of Brown University, Providence, RI.
 Michael Blundin, MD, Department of Medicine, Alpert Medical School of Brown University, Providence, RI.
 Debasree Banerjee, MD, MS, Department of Medicine, Alpert Medical School of Brown University, Providence, RI.

Correspondence

Debasree Banerjee, MD, MS
 Division of Pulmonary, Critical Care and Sleep Medicine
 Rhode Island Hospital
 593 Eddy Street, POB Suite 224
 Providence, RI 02903
 401-444-4191
 Fax 401-444-0094
debasree_banerjee@brown.edu

Diagnosis and Management of Idiopathic Pulmonary Fibrosis

JULIA K. MUNCHEL, MD; BARRY S. SHEA, MD

ABSTRACT

Idiopathic pulmonary fibrosis (IPF) is the most common of the idiopathic interstitial pneumonias. Its signs and symptoms are relatively non-specific, and patients often present with chronic cough, progressive dyspnea, resting or exertional hypoxemia, and inspiratory crackles on lung auscultation. Definitive diagnosis requires the exclusion of known causes of pulmonary fibrosis and identification of the usual interstitial pneumonia (UIP) pattern of disease either on high-resolution computed tomography (HRCT) scan of the chest or on surgical lung biopsy. Multidisciplinary discussion involving pulmonologists, radiologists, and pathologists with expertise in the diagnosis of IPF and other forms of interstitial lung disease is recommended and often required. Management focuses on anti-fibrotic therapy and early referral to lung transplant centers for those who are candidates. This review will discuss the current recommendations for the diagnosis, prognostication, and management of patients with IPF.

KEYWORDS: idiopathic pulmonary fibrosis (IPF), cryptogenic fibrosing alveolitis, usual interstitial pneumonia (UIP), interstitial lung disease (ILD), idiopathic interstitial pneumonia (IIP), diffuse parenchymal lung diseases (DPLD)

INTRODUCTION

History, Epidemiology, and Pathogenesis

Idiopathic pulmonary fibrosis (IPF) is a progressive, fibrosing interstitial lung disease of an uncertain etiology and a poorly understood pathogenesis.¹ It is the most common of the idiopathic interstitial pneumonias (IIPs) and accounts for 20% of all interstitial lung disease (ILD).^{2,3} IPF was first described in the modern literature in 1935 as “fulminating diffuse interstitial fibrosis of the lungs” by Louis Hamman and Arnold Rich and was subsequently coined “Hamman-Rich Syndrome.”⁴ By the 1960s the term IPF was increasingly being used, but it was not until 1998 when Katzenstein and Myers proposed a classification scheme of IIPs that the diagnosis of IPF was exclusively reserved for those individuals with the usual interstitial pneumonia (UIP) pattern on lung biopsy.⁵

This classification scheme was formally adopted by international societies in 1999, resulting in publication of the first international consensus statement on the diagnosis and management of IPF.⁶

Precise estimates of the incidence and prevalence of IPF are difficult to determine, but appear to vary considerably between countries and regions for reasons that remain unclear.^{1,7} In the U.S., recent estimates suggest an incidence of 7–17 per 100,000 person years and incidence and mortality rates appear to be increasing over time worldwide.^{7,8}

IPF is more common in men, current or former cigarette smokers, and in occupations with a high level of inorganic dust exposure.^{1,8} Aging, however, is by far the greatest risk factor.⁸ Although some individuals can be diagnosed as young as 50 years old, the median age at the time of diagnosis is 66 years old and incidence, prevalence, and mortality all increase with increasing age.^{7,9} Genetic factors also appear to play an important role, as both common and rare genetic variants have been associated with the development of IPF, and up to 20% of cases may in fact be familial.¹⁰ Indeed, IPF is increasingly thought of as the result of a complex interplay between aging, host susceptibility (i.e. genetics and epigenetics), and environmental factors.¹¹ The specific relationships between these factors have not been fully elucidated, but the end result appears to be the development of an aberrant, or over-exuberant, wound healing response to repetitive microscopic lung injuries.^{12,13} Many possible causes of microscopic injury have been theorized and include viral infections, gastroesophageal reflux, inhaled particulates, or other environmental exposures.^{12,13}

DIAGNOSIS

The presentation of patients with IPF is relatively non-specific with insidious onset of dyspnea on exertion, non-productive cough, and inspiratory crackles on lung exam.^{2,12,14} Systemic symptoms that would indicate a multisystem disease are not common and if present should raise suspicion for an alternative diagnosis.¹⁵ Clubbing may be present but has only been reported in 25–50% of patients.^{2,12} On pulmonary function testing patients are most commonly found to have restriction with a reduced diffusion capacity, but these changes can at times be mild, particularly in early disease.¹ In contrast, virtually all patients have abnormal chest

imaging on presentation.¹⁵ Conventional chest x-ray (CXR) shows reticulonodular opacities that are typically bilateral, symmetric, and lower lung zone predominant. Occasionally the disease can be asymmetric or unilateral or can lack the typical apico-basilar gradient.¹⁵

Definitive diagnosis first requires the exclusion of any known causes of ILD such as connective tissue disease, drug toxicity, or environmental exposures.¹⁴ Careful history taking is critical with special attention paid to exposures, co-morbidities, medication use, environmental exposures, and family history in order to exclude other etiologies as mentioned above.^{1,15} Laboratory findings are generally non-specific, but can be helpful in ruling out alternative diagnoses such as connective tissue diseases.¹⁵ High resolution computed tomography (HRCT) of the chest plays a central role in the diagnosis of IPF. The characteristic pattern on HRCT consists of bilateral, lower lung zone predominant reticular opacities and honeycombing.¹ Honeycombing refers to aggregates of subpleural, thick-walled cysts typically <1 cm in diameter.^{1,14} Architectural distortion with traction bronchiectasis and bronchiolectasis is also frequently seen.¹⁴ When this typical pattern is seen on HRCT it is 90–100% specific for histologic UIP and in these cases a lung biopsy is generally not required to confirm the diagnosis.¹⁴ However, in cases where the HRCT lacks honeycombing and/or contains features that are not characteristic of UIP, a histologic diagnosis may be required. A surgical lung biopsy – either via thoracotomy or, more commonly, video-assisted thoracoscopic surgery (VATS) – has historically been required for a histologic diagnosis. Bronchoscopic transbronchial forceps biopsies are currently not recommended because the small size of tissue samples obtained does not allow for adequate assessment of the heterogenous changes seen in UIP.^{2,15} The emerging technique of bronchoscopic cryobiopsy may provide a diagnosis of UIP in some cases, but the exact role of this technique in the diagnostic algorithm for IPF remains unclear.¹⁶ If a biopsy is obtained, the typical UIP pattern consists of patchy fibrosis in a predominantly subpleural/paraseptal distribution along with areas of microscopic honeycombing and fibroblastic foci.¹⁴ Fibroblastic foci are aggregates of proliferating fibroblasts and active myofibroblasts which are felt to be indicative of ongoing lung injury and repair that represent the “leading edge” of fibrosis development.¹⁴ Just as with HRCT, lung biopsy specimens may not show all of the typical features of UIP and/or may show features suggestive of an alternative diagnosis. Accordingly, multidisciplinary discussion is recommended between pulmonologists, radiologists, and pathologists to determine whether or not a diagnosis of IPF can be confirmed based on the combination of clinical features, HRCT, and lung biopsy findings if obtained.^{1,14}

PROGNOSIS

IPF is a progressive disease characterized by gradually worsening shortness of breath and, in most cases, the eventual development of respiratory failure.¹ The average survival is only 3–5 years following diagnosis.^{13,17,18} At the same time, it is a clinically heterogenous disease process with considerable variability in the pace of disease progression between both different individuals with the disease and within any given individual over time.¹⁹ Some patients suffer from rapidly progressive disease with a precipitous decline in lung function, while others may experience only slow, steady decline over many years.²⁰ Accordingly, predicting disease progression can be challenging and there is great interest in identifying characteristics that can predict an individual's disease course.¹⁹ Although some imaging findings, such as presence of traction bronchiectasis, have been found to independently predict mortality, changes in pulmonary function tests over time have been found to be among the most robust predictors.² A decline as small as 5% in percent predicted FVC over the course of 6 months was found to be associated with more than a two-fold increase in risk of death over the subsequent 12 months.¹⁹ Not surprisingly, older age and recent respiratory hospitalizations, including acute exacerbations of IPF, have also been found to portend poorer outcomes.¹⁹

Acute exacerbations of IPF (AE-IPF) can occur and often lead to hospitalization for respiratory failure with a precipitous decline in lung function. The proposed definition of AE-IPF requires: 1) a preexisting or concurrent diagnosis of IPF, 2) acute worsening of symptoms (typically <1 month), 3) imaging findings of bilateral ground-glass opacification and/or consolidation superimposed on a background pattern consistent with UIP, and 4) determination that the deterioration is not fully explained by congestive heart failure or volume overload.²¹ On histology, although biopsy is not required for diagnosis, a pattern of diffuse alveolar damage or organizing pneumonia can be seen superimposed on a background of UIP.¹ The mortality of hospitalized cases of AE-IPF is approximately 50%.^{2,22} Even patients who survive hospitalization for AE-IPF continue to have a poor prognosis, and approximately half of all IPF related mortality occurs after a nonelective respiratory hospitalization.¹⁹ Currently there are no known risk factors for the development of acute exacerbations, other than lower FVC and DLCO at baseline, and these events can occur at any point in the disease course regardless of underlying disease severity.^{2,21} Unfortunately, there are no effective treatments for AE-IPF other than supportive care.²¹ High-dose steroids are currently recommended and are commonly prescribed for AE-IPF, but there have been no randomized controlled trials performed to support this practice.¹

TREATMENT

Initially, therapeutics for IPF were focused on modulating the inflammatory response on the supposition that fibrosis was the end stage manifestation of chronic inflammation in the lung. However, over the last decade this treatment paradigm has shifted due to several studies that demonstrated not only a lack of benefit with immunosuppression, but also the possibility for harm.^{23,24} The most notable of these was the PANTHER study published in 2012, which was a randomized, placebo-controlled trial of combination therapy with prednisone, azathioprine, and N-acetylcysteine (NAC) for the treatment of IPF.²³ This study was halted early due to an increase in all-cause mortality, hospitalizations, and treatment-related serious adverse events.²³ It has been hypothesized that prior observational data supporting the use of immunosuppression for IPF may have been skewed by the inclusion of other forms of IIPs that respond more favorably to anti-inflammatory therapy and have more favorable prognoses.¹⁵

Along with the recognition that anti-inflammatory therapy was ineffective in IPF, there was also growing acceptance that IPF was a disease characterized by abnormal wound healing responses in the lung.¹² Therefore, more recent clinical trials have focused on drugs that target these wound healing responses rather than inflammation. In 2014 the U.S. Food and Drug Administration (FDA) approved two antifibrotic medications, nintedanib and pirfenidone, for the treatment of IPF based on large clinical trials showing that both agents slow the decline in lung function by about 50% per year.^{25,26} Pirfenidone is a pyridine molecule with an unknown mechanism of action, but that is thought to have a multitude of anti-fibrotic, anti-inflammatory, and anti-oxidant effects.¹⁵ It has been shown *in vitro* to block growth factor simulated collagen synthesis, extracellular matrix (ECM) secretion, and fibroblast proliferation.^{13,15} Nintedanib is a small molecule inhibitor of several receptor tyrosine kinases, including fibroblast growth factor (FGF), platelet-derived growth factor (PDGF), and vascular endothelial growth factor (VEGF) receptors, and it also appears to inhibit fibroblast activation and ECM synthesis.¹³ Although neither of these drugs are curative for IPF, nor have they definitively been shown to prolong survival, they are the first therapies that have been shown to impact the course of this disease. Furthermore, there are a multitude of additional drugs currently being investigated in late phase clinical trials that provide further hope that more effective treatment options are on the horizon.²⁷

Non-pharmacologic therapy for IPF patients consists of supplemental oxygen administration for those who suffer from clinically significant resting or exertional hypoxemia and pulmonary rehabilitation to help preserve and even improve exercise tolerance.¹ Lung transplantation is the only treatment option that offers IPF patients with advanced disease the opportunity for prolonged survival, as

it has been shown to reduce the risk of death at 5 years.^{1,28} Referral for lung transplant evaluation should be considered in all patients with IPF. Unfortunately, many IPF patients are ineligible for lung transplant due to advanced age and/or co-morbid conditions at the time of presentation.¹⁵

CONCLUSION

IPF is a chronic lung disease characterized by the progressive accumulation of scar tissue (fibrosis) in the lungs, leading to impaired gas exchange, difficulty breathing, and eventually death. IPF symptoms are non-specific and generally consist of insidious onset of dyspnea on exertion and chronic coughing. The diagnosis requires the identification of a UIP pattern of disease on HRCT scan and/or surgical lung biopsy and the exclusion of known causes of pulmonary fibrosis. Anti-fibrotic medications, namely pirfenidone and nintedanib, have been shown to slow disease progression in IPF and are now the mainstays of treatment along with nonpharmacologic therapies such as supplemental oxygen and pulmonary rehabilitation. Lung transplantation is the only intervention that has been shown to reduce mortality in IPF, but unfortunately many patients are ineligible due to advanced age and co-morbidities.

References

1. Raghu G, Collard HR, Egan JJ, et al. ATS/ERS/JRS/ALAT Committee on Idiopathic Pulmonary Fibrosis. An official ATS/ERS/JRS/ALAT statement: idiopathic pulmonary fibrosis: evidence-based guidelines for diagnosis and management. *Am J Respir Crit Care Med*. 2011 Mar 15;183(6):788-824. doi: 10.1164/rccm.2009-040GL.
2. Sgalla G, Biffi A, Richeldi L. Idiopathic pulmonary fibrosis: Diagnosis, epidemiology and natural history. *Respirology*. 2016 Apr;21(3):427-37. doi: 10.1111/resp.12683.
3. Marshall DC, Saliccioli JD, Shea BS et al. Trends in mortality from idiopathic pulmonary fibrosis in the European Union: an observational study of the WHO mortality database from 2001-2013. *Eur Respir J*. 2018 Jan 18;51(1):1701603. doi: 10.1183/13993003.01603-2017.
4. Hamman L, Rich AR. Fulminating Diffuse Interstitial Fibrosis of the Lungs. *Trans Am Clin Climatol Assoc*. 1935;51:154-63.
5. Katzenstein AL, Myers JL. Idiopathic pulmonary fibrosis: clinical relevance of pathologic classification. *Am J Respir Crit Care Med*. 1998 Apr;157(4 Pt 1):1301-15. doi: 10.1164/ajrccm.157.4.9707039.
6. American Thoracic Society. Idiopathic pulmonary fibrosis: diagnosis and treatment. International consensus statement. American Thoracic Society (ATS), and the European Respiratory Society (ERS). *Am J Respir Crit Care Med*. 2000 Feb;161(2 Pt 1):646-64. doi: 10.1164/ajrccm.161.2.ats3-00.
7. Hutchinson J, Fogarty A, Hubbard R, et al. Global incidence and mortality of idiopathic pulmonary fibrosis: a systematic review. *Eur Respir J*. 2015 Sep;46(3):795-806. doi: 10.1183/09031936.00185114.
8. Ley B, Collard HR. Epidemiology of idiopathic pulmonary fibrosis. *Clin Epidemiol*. 2013 Nov 25;5:483-92. doi: 10.2147/CLEP.S54815.
9. Marshall DC, Saliccioli JD, Shea BS, et al. Trends in mortality from idiopathic pulmonary fibrosis in the European Union: an observational study of the WHO mortality database

- from 2001-2013. *Eur Respir J*. 2018 Jan 18;51(1):1701603. doi: 10.1183/13993003.01603-2017.
10. Kropski JA, Blackwell TS, Loyd JE. The genetic basis of idiopathic pulmonary fibrosis. *Eur Respir J*. 2015 Jun;45(6):1717-27. doi: 10.1183/09031936.00163814.
 11. Pardo A, Selman M. Lung Fibroblasts, Aging, and Idiopathic Pulmonary Fibrosis. *Ann Am Thorac Soc*. 2016 Dec;13 Suppl 5:S417-S421. doi: 10.1513/AnnalsATS.201605-341AW.
 12. Selman M, King TE, Pardo A; American Thoracic Society; European Respiratory Society; American College of Chest Physicians. Idiopathic pulmonary fibrosis: prevailing and evolving hypotheses about its pathogenesis and implications for therapy. *Ann Intern Med*. 2001 Jan 16;134(2):136-51. doi: 10.7326/0003-4819-134-2-200101160-00015.
 13. Ahluwalia N, Shea BS, Tager AM. New therapeutic targets in idiopathic pulmonary fibrosis. Aiming to rein in runaway wound-healing responses. *Am J Respir Crit Care Med*. 2014 Oct 15;190(8):867-78. doi: 10.1164/rccm.201403-0509PP.
 14. Raghu G, Remy-Jardin M, Myers JL, et al; American Thoracic Society, European Respiratory Society, Japanese Respiratory Society, and Latin American Thoracic Society. Diagnosis of Idiopathic Pulmonary Fibrosis. An Official ATS/ERS/JRS/ALAT Clinical Practice Guideline. *Am J Respir Crit Care Med*. 2018 Sep 1;198(5):e44-e68.
 15. Gross TJ, Hunninghake GW. Idiopathic pulmonary fibrosis. *N Engl J Med*. 2001 Aug 16;345(7):517-25. doi: 10.1056/NEJMra003200.
 16. Troy LK, Grainge C, Corte TJ, et al; Cryobiopsy versus Open Lung biopsy in the Diagnosis of Interstitial lung disease alliance (COLDICE) Investigators. Diagnostic accuracy of transbronchial lung cryobiopsy for interstitial lung disease diagnosis (COLDICE): a prospective, comparative study. *Lancet Respir Med*. 2020 Feb;8(2):171-181. doi: 10.1016/S2213-2600(19)30342-X.
 17. Raghu G, Chen SY, Yeh WS, et al. Idiopathic pulmonary fibrosis in US Medicare beneficiaries aged 65 years and older: incidence, prevalence, and survival, 2001-11. *Lancet Respir Med*. 2014 Jul;2(7):566-72. doi: 10.1016/S2213-2600(14)70101-8. Epub 2014 May 27. Erratum in: *Lancet Respir Med*. 2014 Jul;2(7):e12. PMID: 24875841.
 18. Kaunisto J, Salomaa ER, Hodgson U, et al. Demographics and survival of patients with idiopathic pulmonary fibrosis in the FinnishIPF registry. *ERJ Open Res*. 2019 Jul 8;5(3):00170-2018. doi: 10.1183/23120541.00170-2018.
 19. du Bois RM, Weycker D, Albera C, et al. Ascertainment of individual risk of mortality for patients with idiopathic pulmonary fibrosis. *Am J Respir Crit Care Med*. 2011 Aug 15;184(4):459-66. doi: 10.1164/rccm.201011-1790OC.
 20. Ley B, Collard HR, King TE Jr. Clinical course and prediction of survival in idiopathic pulmonary fibrosis. *Am J Respir Crit Care Med*. 2011 Feb 15;183(4):431-40. doi: 10.1164/rccm.201006-0894CI.
 21. Collard HR, Ryerson CJ, Corte TJ, et al. Acute Exacerbation of Idiopathic Pulmonary Fibrosis. An International Working Group Report. *Am J Respir Crit Care Med*. 2016 Aug 1;194(3):265-75. doi: 10.1164/rccm.201604-0801CI.
 22. Collard HR, Moore BB, Flaherty KR, et al; Idiopathic Pulmonary Fibrosis Clinical Research Network Investigators. Acute exacerbations of idiopathic pulmonary fibrosis. *Am J Respir Crit Care Med*. 2007 Oct 1;176(7):636-43. doi: 10.1164/rccm.200703-463PP.
 23. Idiopathic Pulmonary Fibrosis Clinical Research Network, Raghu G, Anstrom KJ, King TE Jr, et al. Prednisone, azathioprine, and N-acetylcysteine for pulmonary fibrosis. *N Engl J Med*. 2012 May 24;366(21):1968-77. doi: 10.1056/NEJMoa1113354.
 24. Collard HR, Ryu JH, Douglas WW, et al. Combined corticosteroid and cyclophosphamide therapy does not alter survival in idiopathic pulmonary fibrosis. *Chest*. 2004 Jun;125(6):2169-74. doi: 10.1378/chest.125.6.2169.
 25. Richeldi L, du Bois RM, Raghu G, et al; INPULSIS Trial Investigators. Efficacy and safety of nintedanib in idiopathic pulmonary fibrosis. *N Engl J Med*. 2014 May 29;370(22):2071-82. doi: 10.1056/NEJMoa1402584.
 26. King TE Jr, Bradford WZ, Castro-Bernardini S, et al; ASCEND Study Group. A phase 3 trial of pirfenidone in patients with idiopathic pulmonary fibrosis. *N Engl J Med*. 2014 May 29;370(22):2083-92. doi: 10.1056/NEJMoa1402582.
 27. Trachalaki A, Irfan M, Wells AU. Pharmacological management of Idiopathic Pulmonary Fibrosis: current and emerging options. *Expert Opin Pharmacother*. 2021 Feb;22(2):191-204. doi: 10.1080/14656566.2020.1822326.
 28. Thabut G, Mal H, Castier Y, et al. Survival benefit of lung transplantation for patients with idiopathic pulmonary fibrosis. *J Thorac Cardiovasc Surg*. 2003 Aug;126(2):469-75. doi: 10.1016/s0022-5223(03)00600-7.

Authors

Julia K. Munchel, MD, Division of Pulmonary, Critical Care and Sleep Medicine, Rhode Island Hospital and Alpert Medical School of Brown University, Providence, RI.

Barry S. Shea, MD, Division of Pulmonary, Critical Care and Sleep Medicine, Rhode Island Hospital and Alpert Medical School of Brown University, Providence, RI.

Correspondence

Julia K. Munchel, MD

Division of Pulmonary and Critical Care Medicine

Alpert Medical School of Brown University

Rhode Island Hospital

593 Eddy Street, POB 224

Providence, RI 02903

julia_munchel@brown.edu

Diagnosis of Pulmonary Hypertension

NAVNEET SINGH, MD; CHRISTOPHER J. MULLIN, MD, MHS

ABSTRACT

Pulmonary hypertension (PH) is a chronic disease of elevated pulmonary artery pressure that can result from pulmonary vascular diseases or complicate left heart and lung disease. Pulmonary arterial hypertension (PAH) is a rare pulmonary artery vasculopathy that leads to progressive right heart failure and death. Timely and accurate diagnosis of PH is paramount, given the increased morbidity and mortality, but can be challenging given the nonspecific nature of the presenting symptoms and the many potential causative or contributing conditions. The diagnosis of PH remains clinical and the initial workup uses history, physical exam, and echocardiography to evaluate likelihood of disease, followed by characterization of left heart and lung disease and the appropriate evaluation for chronic thromboembolic disease. A right heart catheterization is requisite for the diagnosis and thus early referral to a PH expert center is strongly recommended, particularly for patients with high-risk features and in high-risk populations.

KEYWORDS: pulmonary hypertension, pulmonary arterial hypertension, right ventricle, right heart catheterization

INTRODUCTION

Pulmonary hypertension (PH) is defined as a resting mean pulmonary artery pressure (mPAP) greater than 20 mmHg¹, although prior guidelines and consensus statements used a definition of mPAP ≥ 25 mmHg to define the disease.^{2,3} This recent change in definition was based on the observations that 20 mmHg is the upper limit of normal in healthy subjects and an mPAP between 21 and 24 mmHg is associated with poorer outcomes in certain disease states.¹ Pulmonary hypertension can often complicate left heart and lung disease, and when it does is associated with increased mortality. Pulmonary arterial hypertension (PAH) is a rare disease characterized by medial hypertrophy, intimal and adventitial fibrosis, in situ thrombosis, and plexiform lesions of the distal muscular pulmonary arteries,⁴ which result in a rise in pulmonary vascular resistance (PVR) and pulmonary artery pressures, leading to progressive right heart failure and death. PAH is defined by presence of precapillary PH (mPAP

>20 mmHg, pulmonary artery wedge pressure (PAWP) ≤ 15 mmHg and PVR ≥ 3 WU) in the absence of significant left heart, lung, or chronic thromboembolic disease.

A diagnosis of pulmonary hypertension is often suspected in the setting of exertional dyspnea and suggestive findings on echocardiogram. The diagnostic questions posed in the initial evaluation of a patient in whom pulmonary hypertension is suspected are: does the patient have PH?, and if so, what is the cause and how severe is the PH? As such, an evaluation to correctly diagnose pulmonary hypertension requires 1) clinical suspicion based on history and examination, 2) echocardiography to evaluate for likelihood of PH, 3) characterization of the extent of any lung and left heart disease, 4) thorough evaluation for chronic thromboembolic disease and conditions associated with PAH, and 5) referral to a center with PH expertise for evaluation that typically includes right heart catheterization to define hemodynamics. Given the significant morbidity and mortality associated with both PH and PAH, seeking PH expertise early in the diagnostic evaluation is advised, particularly for patients with high-risk features.

CLINICAL CLASSIFICATION

Pulmonary hypertension is classified into five groups, based on the World Symposium on Pulmonary Hypertension (WSPH) classification scheme, presented in **Table 1**. The purpose of this classification scheme is to group clinical conditions that share similar pathophysiological mechanisms, clinical presentation, hemodynamic characteristics, and therapeutic management.¹ WSPH Group 1 PAH is defined as precapillary PH in the absence of significant left heart, lung, or chronic thromboembolic disease. WSPH Group 2 PH is defined by presence of post-capillary PH (mPAP >20 mmHg and PAWP ≥ 15 mmHg), and WSPH Group 3 PH is defined by mPAP 21–24 mmHg with PVR ≥ 3 WU, or mPAP ≥ 25 mmHg.⁵ WSPH Group 4 PH consists predominantly of chronic thromboembolic PH (CTEPH), which is defined by precapillary PH in the presence of chronic or organized flow-limiting thrombi/emboli in the elastic pulmonary arteries (PAs) after at least 3 months of effective anticoagulation. Finally, WSPH Group 5 PH includes a variety of diseases with unclear or multifactorial mechanisms. Although this is a heterogeneous and relatively understudied group

of diseases, it still represents a significant portion of disease seen in pulmonary hypertension centers. The clinical classification scheme provides a framework that allows for a comprehensive differential diagnosis in the evaluation of pulmonary hypertension. It should be noted that most of the WSPH Groups are based upon specific hemodynamic definitions, which emphasizes the importance of right heart catheterization in the diagnosis of pulmonary hypertension.

Table 1. World Symposium on Pulmonary Hypertension (WSPH) Classification of Pulmonary Hypertension

Group 1: Pulmonary arterial hypertension (PAH)
1.1 Idiopathic PAH
1.2 Heritable PAH
1.3 Drug- and Toxin-Induced PAH
1.4 PAH associated with:
1.4.1 Connective tissue disease
1.4.2 Human immunodeficiency virus infection
1.4.3 Portal hypertension
1.4.4 Congenital heart disease
1.4.5 Schistosomiasis
1.5 Long-term responders to calcium channel blockers
1.6 PAH with overt features of venous/capillary involvement (pulmonary veno-occlusive disease or pulmonary capillary hemangiomatosis)
1.7 Persistent pulmonary hypertension of the newborn
Group 2: Pulmonary hypertension due to left heart disease
2.1 Heart failure with preserved left ventricular ejection fraction
2.2 Heart failure with reduced left ventricular ejection fraction
2.3 Valvular heart disease
2.4 Congenital/acquired cardiovascular conditions leading to post-capillary PH
Group 3: Pulmonary hypertension due to lung diseases and/or hypoxia
3.1 Obstructive lung disease
3.2 Restrictive lung disease
3.3 Other lung diseases with mixed restrictive and obstructive pattern
3.4 Hypoxia without lung disease
3.5 Developmental lung diseases
Group 4: Pulmonary hypertension due to pulmonary arterial obstructions
4.1 Chronic thromboembolic pulmonary hypertension
4.2 Other pulmonary artery obstructions: sarcoma, other malignant or non-malignant tumors, arteritis without connective tissue disease, congenital pulmonary artery stenosis, parasites
Group 5: Pulmonary hypertension with unclear and/or multifactorial mechanisms
5.1 Hematologic disorders: chronic hemolytic anemia, myeloproliferative disorders
5.2 Systemic and metabolic disorders: sarcoidosis, pulmonary Langerhans cell histiocytosis, glycogen storage disease, Gaucher disease, neurofibromatosis.
5.3 Others: chronic renal failure with or without hemodialysis, fibrosing mediastinitis
5.4 Complex congenital heart disease

Adapted from Simonneau, et al. 2019.¹

However, the classification of an individual patient’s PH combines hemodynamic data with a comprehensive clinical evaluation.

EPIDEMIOLOGY

Pulmonary arterial hypertension (PAH) remains an uncommon disease; however, published estimates of epidemiology vary. This is likely due to geographic, racial, ethnic, and socioeconomic differences in prevalence, presentation, and outcomes, with variations in reporting and tracking among countries. Ranges for incidence are 1.5–3.2 persons per million per year and for prevalence are 12.4–268 persons per million, with a noted greater prevalence in data from nationalized systematic registries as compared to non-systematic registries.⁶ Pulmonary hypertension (PH) as a whole also is relatively uncommon, with an incidence of 28.7 cases per 100,000 per year. However, the prevalence of the disease is reported to be increasing from 99.8 to 127.3 cases per 100,000 population from 1993 to 2012.⁷ This is likely due to the increasing awareness of the disease, improvement in screening of high-risk populations, and greater availability of non-invasive diagnostic and screening tools. Importantly, WSPH Group 2 PH is the most common form of PH. One population-based cohort study found that Group 2 PH accounted for 34.2% of PH cases alone and another 29.3% of cases when combined with lung disease. PH due to left heart disease has contributed most to the increasing prevalence in the adult population, accounting for over 75% of all new cases.⁷

The incident population of PAH continues to be predominantly of female sex (62.1%) and younger at index date (mean age 65.1 years) as compared to PH (54.1% female sex and mean age 72.9 years).⁷ This follows with the observation that new PH diagnoses are largely driven by those individuals with pre-existing left-sided heart and lung disease, whereas PAH is a primary pulmonary artery vasculopathy with a unique presentation and clinical course.

HISTORY AND PHYSICAL EXAM

Although hemodynamic evaluation via right heart catheterization (RHC) is a crucial part of the evaluation process, the diagnosis of pulmonary hypertension remains a clinical one. Thus, a thorough history and physical exam is necessary prior to diagnostic interventions.

The most common presenting symptom in patients with pulmonary hypertension is dyspnea on exertion or a decrease in exercise capacity. Given the nonspecific nature of these symptoms, it is important to evaluate each patient for alternate etiologies of dyspnea, including obstructive airways disease and left ventricular or valvular dysfunction, among others. Symptoms including orthopnea and lower extremity edema are typically signs of advanced disease as they

indicate right ventricular dysfunction, which is a known late sequela of the disease.⁸ When identified in a patient with lack of echocardiographic evidence of right-ventricular dysfunction, alternate diagnoses should be considered. Concerning symptoms such as dizziness or lightheadedness with exertion or syncope are known high-risk features in patients with right ventricular failure and should prompt an expedited workup.⁸

Of importance is the level of clinical suspicion that a patient may have WSPH Group 1 PAH or Group 4 PH versus Groups 2, 3, or 5 PH. The reason for this distinction is that Groups 2, 3, and 5 typically rely on treating the underlying disease and supportive therapy, whereas Groups 1 and 4 may require additional diagnostic interventions and the mainstay of treatment remains pulmonary vasodilators.

The historical factors that may raise suspicion for the presence of Group 1 PAH include a family history of PAH, history of exposure to particular drugs or toxins known to cause pulmonary arterial hypertension, including certain chemotherapeutic agents, anorexigens and methamphetamine,⁸ a personal or family history of connective tissue disease (particularly scleroderma, lupus, and mixed connective tissue disease), known history of HIV infection, chronic liver disease with portal hypertension, and a history of congenital heart disease. A personal or family history of prior venous thromboembolism may raise suspicion for Group 4 PH, particularly CTEPH. However, lack of this history should not preclude additional diagnostic workup as the incidence of CTEPH following pulmonary embolism varies in the literature from 15% to 33% in Japanese cohorts^{8,9} to 75% in a European and Canadian cohort.¹⁰ Additional historical factors that may inform a diagnosis of Groups 2, 3, and 5 PH include general screening for left-sided or valvular heart diseases, obstructive airways diseases, sleep-disordered breathing, and interstitial lung diseases.

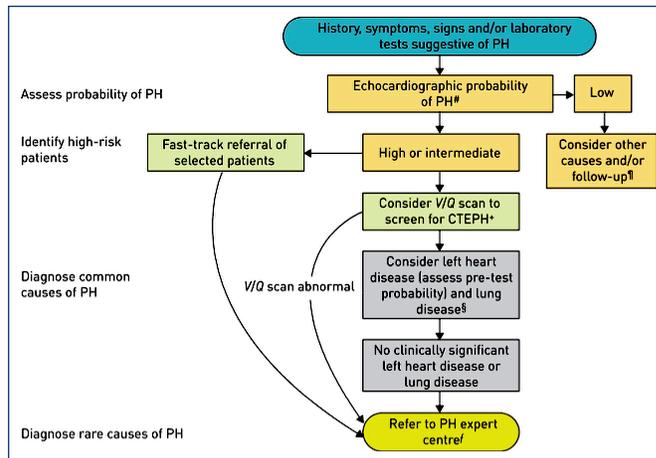
On physical exam, a loud pulmonic component of the second heart sound (P2), a tricuspid regurgitation murmur, and a palpable right ventricular heave may be identified. An increased jugular venous pulsation, hepatojugular reflex, and peripheral edema can all be seen with worsening right-ventricular function and failure. Care should be taken to also examine the patient for signs of related diagnoses. For example, an exam for undiagnosed connective tissue diseases may include evaluating for sclerodactyly, skin thickening, digital ulceration, telangiectasias, rashes, and joint edema.

DIAGNOSTIC ALGORITHMS

The recommended diagnostic algorithm for pulmonary hypertension (Figure 1) is largely dependent on whether the workup is being performed outside a PH expert center, and if so, the probability of PH based on available data and thus the need for expedited referral. Echocardiographic signs that raise suspicion for PH are detailed below and in Table 3.

These signs and high-risk symptoms (e.g., exertional dizziness, syncope) should prompt expedited referral to a PH expert center.

Figure 1. Diagnostic Algorithm for the Diagnosis of Pulmonary Hypertension Outside a Pulmonary Hypertension Expert Center



PH= pulmonary hypertension. CTEPH = chronic thromboembolic PH. Adapted from Frost, et al. 2019.⁸

Transthoracic Echocardiography

Echocardiography is the most important non-invasive screening tool in the evaluation for PH. High-risk echocardiographic features should be used to expedite workup and referral for right heart catheterization (RHC), which remains mandatory to establish the diagnosis.

Based on echocardiographic data from healthy individuals at rest and expert opinion, the tricuspid regurgitation velocity (which is used to calculate the pulmonary artery systolic pressure or PASP) and the presence or absence of other signs of echocardiographic PH are used together to establish the echocardiographic probability of PH (Tables 2 and 3). Other signs of PH on echocardiography include right ventricular enlargement, decreased right ventricular systolic function, flattening of the interventricular septum, right atrial enlargement, lack of respiratory variation in the inferior vena cava, and the diameter of the pulmonary artery.¹¹⁻¹³

Table 2. Echocardiographic probability of Pulmonary Hypertension in symptomatic patients with a suspicion of Pulmonary Hypertension

Peak tricuspid regurgitation velocity (m/s)	Presence of other echo "PH signs" *	Echocardiographic probability of PH
≤ 2.8 or not measurable	No	Low
≤ 2.8 or not measurable	Yes	Intermediate
2.9 – 3.4	No	
2.9 – 3.4	Yes	High
> 3.4	Not required	

PH = pulmonary hypertension. *See Table 3. Adapted from Galie, et al. 2015.²

Table 3. Echocardiographic Signs Suggesting Pulmonary Hypertension

The ventricles	Pulmonary artery	Inferior vena cava and right atrium
Right ventricle/left ventricle basal diameter ratio >1.0	Right ventricular outflow Doppler acceleration time <105 msec and/or midsystolic notching	Inferior cava diameter >21 mm with decreased inspiratory collapse (<50 % with a sniff or <20 % with quiet inspiration)
Flattening of the interventricular septum (left ventricular eccentricity index > 1.1 in systole and/or diastole)	Early diastolic pulmonary regurgitation velocity >2.2 m/sec	Right atrial area (end-systole) >18 cm ²
	PA diameter >25 mm	

PA = pulmonary artery. Adapted from Galìè, et al. 2015.²

Electrocardiography

Though a normal electrocardiograph (ECG) does not exclude the diagnosis of PH, changes may provide helpful clues. When present, ECG changes are associated with a worse prognosis and so may be used with other data to expedite a patient's workup.^{14,15} Changes typically seen in the ECGs of patients with PH include p pulmonale, right ventricular (RV) strain pattern, RV hypertrophy, and right bundle branch block.

Laboratory Testing

Routine hematology, biochemical, and thyroid testing are required for all patients being evaluated for pulmonary hypertension. Routine blood tests may reveal nonspecific signs such as hepatic congestion from right ventricular failure. An elevated brain natriuretic peptide (BNP) or N-terminal pro-BNP is associated with worse outcomes.¹⁶

Serological assessment may be helpful in differentiating subtypes of the disease, thus all patients undergoing evaluation for PH require screening for connective tissue disease (CTD), HIV, and hepatitis. Because patients with CTD on the scleroderma spectrum are at particularly high risk for development of PAH, antinuclear antibodies (ANAs) are recommended in the initial workup for PH, although it should be noted that low titer positives (1:80) are frequent in patients who lack other convincing features of CTD.

Pulmonary Function Testing

Clinical history and symptoms should guide the need for pulmonary function tests (PFTs). These tests should include total lung capacity and diffusing capacity of the lung for carbon monoxide (DLCO). While airways obstruction or restrictive physiology can be observed in Group 3 PH, patients with Group 1 PAH may demonstrate a mild restrictive component and a mild to moderate reduction in DLCO.¹⁷ Marked reductions in DLCO may indicate pulmonary veno-occlusive disease (PVOD)/pulmonary capillary hemangiomatosis (PCH).¹⁸

Ventilation/Perfusion (V/Q) Scan

A V/Q scan to screen for chronic thromboembolic disease should be performed in all patients being evaluated for PH. CTEPH is likely underdiagnosed and remains elusive, in part due to the underutilization of V/Q scanning

despite guideline recommendations.^{19,20} A normal V/Q scan excludes CTEPH with a sensitivity of 90–100% and a specificity of 94–100%^{21,22} and so is the preferred test for CTEPH screening.^{19,23} An abnormal V/Q scan should prompt referral to a PH expert center as additional diagnostic interventions such as pulmonary angiography may need to be considered as part of the diagnostic evaluation.

Chest Computed Tomography (CT)

Chest CT is not a diagnostic tool for PH; however, several features may be suggestive. These include an enlarged pulmonary artery (diameter ≥ 29 mm), right ventricular dilation, right atrial dilation, and a main pulmonary artery/ascending aorta diameter ratio ≥ 1 .²⁴ An examination of the lung parenchyma may also be helpful in identifying parenchymal lung diseases responsible for Group 3 PH.

SCREENING IN HIGH-RISK POPULATIONS

Scleroderma (Systemic Sclerosis) and Scleroderma Spectrum

The incidence of PAH in connective tissue diseases on the scleroderma spectrum is estimated between 5–12%, which is substantially more than the population at large.^{25,26} Current guidelines recommend annual screening for PAH in patients with systemic sclerosis (SSc) with an uncorrected DLCO < 80% predicted.^{2,3,27} Recommended screening tools include the DETECT algorithm, TTE or FVC/DLCO ratio > 1.6, and NT-proBNP greater than 2-fold the upper limit of normal.⁸

Human Immunodeficiency Virus (HIV)

While the true incidence of PAH in persons infected with HIV is not clear, ongoing studies suggest that it may be higher than previously reported.⁸ In order to enrich the population that would benefit from routine screening, additional concomitant risk factors that increase the risk of development of PAH in HIV-positive individuals should be used to guide selection of asymptomatic patients for screening. These include female sex, intravenous drug or cocaine use, hepatitis C virus infection, origin from a high-prevalence country, known negative regulatory factor (Nef) or transactivator of transcription (Tat) HIV proteins, and Black ethnicity in United States patients.^{28–33}

RIGHT HEART CATHETERIZATION

As the diagnosis and classification of pulmonary hypertension centers on hemodynamic definitions, correct performance and interpretation of right heart catheterization is essential for the diagnosis of PH. Comprehensive descriptions of RHC for the diagnosis of PH are reviewed elsewhere.³⁴ Proper set up for RHC requires appropriate calibration of all equipment, and leveling of transducers to the level of the left atrium – the midsagittal line in a supine patient.³⁵ Pressure measurements are performed during spontaneous respirations, with resting measurements made at end expiration. Correct measurement of PAWP during RHC is critical, as this is a measure prone to error by under- or over-wedging, and is necessary to distinguish between pre- and post-capillary PH. PAWP is typically measured at end expiration; however, measurements averaged over multiple respiratory cycles may be useful in patients with obesity or chronic obstructive pulmonary disease.

Similarly, measurement of cardiac output is critical in the diagnosis of PH, to calculate pulmonary vascular resistance and assess the severity of PH and any cardiac dysfunction. The thermodilution method of cardiac output measurement is the recommended technique² and requires a Swan Ganz catheter with a thermistor tip. Although there may be concerns about potential inaccuracy in the setting of low cardiac output, and/or significant tricuspid regurgitation, the thermodilution method has been shown to be accurate in these circumstances in pulmonary hypertension.³⁶ Measurement of central venous and pulmonary arterial saturations should be performed to evaluate for the presence of a left to right cardiac shunt. Vasoreactivity testing is performed by administration of a pulmonary vasodilator – typically inhaled nitric oxide (although intravenous epoprostenol, intravenous adenosine or inhaled iloprost can also be used) during RHC. A positive response is defined by a decrease in mPAP by ≥ 10 mmHg to mPAP ≤ 40 mmHg without a decrease in cardiac output.¹ This should be performed in all patients with suspected or confirmed idiopathic PAH, heritable PAH, or drug- and toxin-induced PAH, to identify a subset of patients who are likely to benefit from treatment with calcium channel blockers. Lastly, provocative challenges such as exercise or administration of a fluid bolus may be useful in certain clinical settings but should be performed by operators skilled in their performance and interpretation. Given the complexities of hemodynamic evaluation for the diagnosis and management of PH, RHC should be performed by an operator with skill and experience in pulmonary hypertension.

CONCLUSION

The diagnosis of pulmonary hypertension can be challenging given the nonspecific nature of its presentation and multiple potential causes. Careful interpretation of history, physical exam, and echocardiogram is helpful to define the level of

suspicion for the disease. Understanding the clinical classification and epidemiology of PH provides a framework for the differential diagnosis and diagnostic evaluation. Right heart catheterization remains mandatory to define hemodynamics and confirm the diagnosis of PH. Early referral to a PH center of expertise is necessary, particularly in patients with high-risk features and in high-risk populations.

References

1. Simonneau G, Montani D, Celermajer DS, Denton CP, Gatzoulis MA, Krowka M, Williams PG, Souza R. Haemodynamic definitions and updated clinical classification of pulmonary hypertension. *European Respiratory Journal*. 2019;53.
2. Galie N, Humbert M, Vachiery J-L, Gibbs S, Lang I, Torbicki A, Simonneau G, Peacock A, Vonk Noordegraaf A, Beghetti M. 2015 ESC/ERS guidelines for the diagnosis and treatment of pulmonary hypertension: the joint task force for the diagnosis and treatment of pulmonary hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS): endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC), International Society for Heart and Lung Transplantation (ISHLT). *European heart journal*. 2016;37:67-119.
3. Hoeper MM, Bogaard HJ, Condliffe R, Frantz R, Khanna D, Kurzyna M, Langleben D, Manes A, Satoh T, Torres F. Definitions and diagnosis of pulmonary hypertension. *Journal of the American College of Cardiology*. 2013;62:D42-D50.
4. Humbert M, Guignabert C, Bonnet S, Dorfmueller P, Klinger JR, Nicolls MR, Olschewski AJ, Pullamsetti SS, Schermuly RT, Stenmark KR. Pathology and pathobiology of pulmonary hypertension: state of the art and research perspectives. *European Respiratory Journal*. 2019;53.
5. Nathan SD, Barbera JA, Gaine SP, Harari S, Martinez FJ, Olschewski H, Olsson KM, Peacock AJ, Pepke-Zaba J, Provencher S. Pulmonary hypertension in chronic lung disease and hypoxia. *European Respiratory Journal*. 2019;53.
6. Leber L, Beaudet A, Muller A. Epidemiology of pulmonary arterial hypertension and chronic thromboembolic pulmonary hypertension: identification of the most accurate estimates from a systematic literature review. *Pulmonary circulation*. 2021;11:2045894020977300.
7. Wijeratne DT, Lajkosz K, Brogly SB, Lougheed MD, Jiang L, Housin A, Barber D, Johnson A, Doliszny KM, Archer SL. Increasing incidence and prevalence of World Health Organization groups 1 to 4 pulmonary hypertension: a population-based cohort study in Ontario, Canada. *Circulation: Cardiovascular Quality and Outcomes*. 2018;11:e003973.
8. Frost A, Badesch D, Gibbs JSR, Gopalan D, Khanna D, Manes A, Oudiz R, Satoh T, Torres F, Torbicki A. Diagnosis of pulmonary hypertension. *European Respiratory Journal*. 2019;53.
9. Ogawa A, Satoh T, Fukuda T, Sugimura K, Fukumoto Y, Emoto N, Yamada N, Yao A, Ando M, Ogino H. Balloon pulmonary angioplasty for chronic thromboembolic pulmonary hypertension: results of a multicenter registry. *Circulation: Cardiovascular Quality and Outcomes*. 2017;10:e004029.
10. Pepke-Zaba J, Delcroix M, Lang I, Mayer E, Jansa P, Ambroz D, Treacy C, D'Armini AM, Morsolini M, Snijder R. Chronic thromboembolic pulmonary hypertension (CTEPH) results from an international prospective registry. *Circulation*. 2011;124:1973-1981.
11. Hellenkamp K, Unsöld B, Mushemi-Blake S, Shah AM, Friede T, Hasenfuß G, Seidler T. Echocardiographic estimation of mean pulmonary artery pressure: a comparison of different approaches to assign the likelihood of pulmonary hypertension. *Journal of the American Society of Echocardiography*. 2018;31:89-98.
12. Magnino C, Omede P, Avenatti E, Presutti D, Iannaccone A, Chiarlo M, Moretti C, Gaita F, Veglio F, Milan A. Inaccuracy of right atrial pressure estimates through inferior vena cava indices. *The American journal of cardiology*. 2017;120:1667-1673.

13. Focardi M, Cameli M, Carbone SF, Massoni A, De Vito R, Lisi M, Mondillo S. Traditional and innovative echocardiographic parameters for the analysis of right ventricular performance in comparison with cardiac magnetic resonance. *European Heart Journal-Cardiovascular Imaging*. 2015;16:47-52.
14. Bossone E, Paciocco G, Iarussi D, Agretto A, Iacono A, Gillespie BW, Rubenfire M. The prognostic role of the ECG in primary pulmonary hypertension. *Chest*. 2002;121:513-518.
15. Henkens IR, Gan CT-J, van Wolferen SA, Hew M, Boonstra A, Twisk JW, Kamp O, van der Wall EE, Schalij MJ, Noordegraaf AV. ECG monitoring of treatment response in pulmonary arterial hypertension patients. *Chest*. 2008;134:1250-1257.
16. Nagaya N, Nishikimi T, Uematsu M, Satoh T, Kyotani S, Sakamaki F, Kakishita M, Fukushima K, Okano Y, Nakanishi N. Plasma brain natriuretic peptide as a prognostic indicator in patients with primary pulmonary hypertension. *Circulation*. 2000;102:865-870.
17. Sun X-G, Hansen JE, Oudiz RJ, Wasserman K. Pulmonary function in primary pulmonary hypertension. *Journal of the American College of Cardiology*. 2003;41:1028-1035.
18. Hadinnapola C, Bleda M, Haimel M, Sreaton N, Swift A, Dorf-müller P, Preston SD, Southwood M, Hernandez-Sanchez J, Martin J. Phenotypic characterization of EIF2AK4 mutation carriers in a large cohort of patients diagnosed clinically with pulmonary arterial hypertension. *Circulation*. 2017;136:2022-2033.
19. McLaughlin VV, Langer A, Tan M, Clements PJ, Oudiz RJ, Tapson VF, Channick RN, Rubin LJ and Initiative PAH-QER. Contemporary trends in the diagnosis and management of pulmonary arterial hypertension: an initiative to close the care gap. *Chest*. 2013;143:324-332.
20. Tapson VF, Platt DM, Xia F, Teal SA, de la Orden M, Divers CH, Satler CA, Joish VN, Channick RN. Monitoring for pulmonary hypertension following pulmonary embolism: the INFORM study. *The American journal of medicine*. 2016;129:978-985. e2.
21. Tunariu N, Gibbs SJ, Win Z, Gin-Sing W, Graham A, Gishen P, Adil A-N. Ventilation-perfusion scintigraphy is more sensitive than multidetector CTPA in detecting chronic thromboembolic pulmonary disease as a treatable cause of pulmonary hypertension. *Journal of nuclear medicine*. 2007;48:680-684.
22. He J, Fang W, Lv B, He J-G, Xiong C-M, Liu Z-H, He Z-X. Diagnosis of chronic thromboembolic pulmonary hypertension: comparison of ventilation/perfusion scanning and multidetector computed tomography pulmonary angiography with pulmonary angiography. *Nuclear medicine communications*. 2012;33:459-463.
23. Kim NH, Delcroix M, Jenkins DP, Channick R, Dartevelle P, Jansa P, Lang I, Madani MM, Ogino H, Pengo V. Chronic thromboembolic pulmonary hypertension. *Journal of the American College of Cardiology*. 2013;62:D92-D99.
24. Shen Y, Wan C, Tian P, Wu Y, Li X, Yang T, An J, Wang T, Chen L, Wen F. CT-base pulmonary artery measurement in the detection of pulmonary hypertension: a meta-analysis and systematic Review. *Medicine*. 2014;93.
25. Avouac J, Airò P, Meune C, Beretta L, Dieude P, Caramaschi P, Tiev K, Cappelli S, Diot E, Vacca A. Prevalence of pulmonary hypertension in systemic sclerosis in European Caucasians and metaanalysis of 5 studies. *The Journal of rheumatology*. 2010;37:2290-2298.
26. Mukerjee D, St George D, Coleiro B, Knight C, Denton C, Davar J, Black C, Coghlan J. Prevalence and outcome in systemic sclerosis associated pulmonary arterial hypertension: application of a registry approach. *Annals of the rheumatic diseases*. 2003;62:1088-1093.
27. Khanna D, Gladue H, Channick R, Chung L, Distler O, Furst DE, Hachulla E, Humbert M, Langleben D, Mathai SC. Recommendations for screening and detection of connective tissue disease-associated pulmonary arterial hypertension. *Arthritis & Rheumatism*. 2013;65:3194-3201.
28. Dhillon NK, Li F, Xue B, Tawfik O, Morgello S, Buch S, Ladner AOB. Effect of cocaine on human immunodeficiency virus-mediated pulmonary endothelial and smooth muscle dysfunction. *American journal of respiratory cell and molecular biology*. 2011;45:40-52.
29. Quezada M, Martin-Carbonero L, Soriano V, Vispo E, Valencia E, Moreno V, de Isla LP, Lennie V, Almeria C, Zamorano JL. Prevalence and risk factors associated with pulmonary hypertension in HIV-infected patients on regular follow-up. *Aids*. 2012;26:1387-1392.
30. Dalvi P, O'Brien-Ladner A, Dhillon NK. Downregulation of bone morphogenetic protein receptor axis during HIV-1 and cocaine-mediated pulmonary smooth muscle hyperplasia: implications for HIV-related pulmonary arterial hypertension. *Arteriosclerosis, thrombosis, and vascular biology*. 2013;33:2585-2595.
31. Sangal RB, Taylor LE, Gillani F, Poppas A, Klinger JR, Ventet-uolo CE. Risk of echocardiographic pulmonary hypertension in individuals with human immunodeficiency virus-hepatitis C virus coinfection. *Annals of the American Thoracic Society*. 2014;11:1553-1559.
32. Rudski LG, Lai WW, Afilalo J, Hua L, Handschumacher MD, Chandrasekaran K, Solomon SD, Louie EK, Schiller NB. Guidelines for the echocardiographic assessment of the right heart in adults: a report from the American Society of Echocardiography: endorsed by the European Association of Echocardiography, a registered branch of the European Society of Cardiology, and the Canadian Society of Echocardiography. *Journal of the American society of echocardiography*. 2010;23:685-713.
33. Schwarze Zander C, Pabst S, Hammerstingl C, Ohlig J, Was-muth J, Boesecke C, Stoffel Wagner B, Carstensen A, Nickenig G, Strassburg C. Pulmonary hypertension in HIV infection: a prospective echocardiographic study. *HIV medicine*. 2015; 16:578-582.
34. Rosenkranz S, Preston IR. Right heart catheterisation: best practice and pitfalls in pulmonary hypertension. *European Respiratory Review*. 2015;24:642-652.
35. Kovacs G, Avian A, Pienn M, Naeije R, Olschewski H. Reading pulmonary vascular pressure tracings. How to handle the problems of zero leveling and respiratory swings. *American journal of respiratory and critical care medicine*. 2014;190:252-257.
36. Hoepfer MM, Maier R, Tongers J, Niedermeyer J, Hohlfeld JM, Hamm M, Fabel H. Determination of cardiac output by the Fick method, thermodilution, and acetylene rebreathing in pulmonary hypertension. *American journal of respiratory and critical care medicine*. 1999;160:535-541.

Authors

Navneet Singh, MD, Division of Pulmonary, Critical Care and Sleep Medicine, Warren Alpert Medical School of Brown University, Providence, RI.

Christopher J. Mullin, MD, MHS, Division of Pulmonary, Critical Care and Sleep Medicine, Warren Alpert Medical School of Brown University, Providence, RI.

Disclosures

None

Correspondence

Christopher J. Mullin, MD, MHS

Division of Pulmonary, Critical Care and Sleep Medicine
Rhode Island Hospital

593 Eddy Street, POB Suite 224

Providence, RI 02903

401-444-2670

Fax 401-444-5914

christopher_mullin@brown.edu

The Evolving Continuum of Diagnosis in the Modern Age of Non-Small Cell Lung Cancer

DANIEL DUSTIN, DO; DOUGLAS MARTIN, MD

ABSTRACT

Lung cancer remains the most common cause of cancer-related deaths in the United States. Traditional treatment of non-small cell lung cancer has included surgical resection for suitable candidates with early stage (I/II) disease and various chemoradiotherapeutic regimens used for advanced disease, for which prognosis has been poor. Since the early 2000s, there has been a revolution in the diagnosis and treatment of non-small cell lung cancer driven by improved diagnostic techniques and therapies targeted to druggable oncogenic drivers or manipulation of the immunologic milieu in the tumor microenvironment. With this has come a need for frequently updated comprehensive data regarding response to treatment and acquired resistance to targeted therapies. In this article, we aim to provide a concise review of the state-of-the-art in lung cancer workup in 2021, with a focus on how molecular data now informs treatment decisions. With the burgeoning use of immunotherapeutic approaches, we will also discuss some of the complications seen, and briefly discuss their management.

KEYWORDS: Non-Small Cell Lung Cancer (NSCLC), Endobronchial Ultrasound (EBUS), Immunotherapy, Driver Mutations, Immune Related Adverse Events

INTRODUCTION

Lung cancer represents 13% of all new cancer diagnoses and accounts for 25% of all cancer deaths.^{1,2} Non-small cell lung cancer (including Adenocarcinoma, Squamous Cell, Large Cell) comprises approximately 85% of all lung cancers. While the introduction of low-dose CT (LDCT) screening holds promise in improving rates of early detection, lung cancer has traditionally presented at an advanced stage in more than 80% of patients. Prognosis for patients with Stage III or IV disease treated with chemoradiotherapeutic regimens has traditionally been dismal with five-year survival rates <25% in stage IIIA.

DIAGNOSIS AND STAGING

Patients may present with a spectrum of disease from asymptomatic with small nodule(s) to severely ill with widely

metastatic or bulky intrathoracic disease. For patients with small nodules (e.g., $\leq 8\text{mm}$), validated guidelines are utilized to guide radiographic evaluation. The Fleischner Society Guidelines apply for incidentally found nodules while the Lung-RADS system is used for screen-detected nodules.^{3,4} The latter differs due to the generally higher-risk characteristics of patients meeting screening criteria and the fact that the default in that population remains one year repeat low-dose screening scan.

The Tumor, Node, Metastasis (TNM) staging system is utilized in non-small cell lung cancer. Tissue acquisition is ideally performed from the area that provides the highest overall stage.⁵ Surgical biopsy and resection are sometimes utilized in appropriate patients with high likelihood of early stage (Stages I/II) NSCLC. Fluorodeoxyglucose (FDG) Positron Emission Tomography (PET) scan is commonly obtained to assess the mediastinum and to assess for the possibility of distant metastases, including to sites such as the adrenal glands or bone. Percutaneous biopsy is commonly performed for lung nodules (particularly peripheral ones), but bronchoscopic techniques guided by magnetic navigation, cone-beam computed tomography (CT), radial ultrasound, and robotic technology have gained an increasing role.⁶ Endosonographic-based sampling techniques (linear endobronchial ultrasound (EBUS) from the tracheobronchial tree or endoscopic ultrasound (EUS) from the gastrointestinal tract) are used in cases of suspected hilar or mediastinal nodal disease and facilitate their fine needle aspiration (FNA) guided by real time ultrasound imaging. Endosonographic techniques are also commonly used to exclude nodal disease prior to surgical resection or (usually in nonsurgical candidates) radiation therapy.⁶ If imaging is suggestive of distant metastases, image-guided biopsy can establish both diagnosis and staging.

In patients without PET-detected extra thoracic disease, mediastinal lymph node sampling is commonly performed. A study by Um et al. demonstrated similar diagnostic yield with EBUS FNA showing a favorable side effect profile compared to mediastinoscopy.⁷ For these reasons, EBUS is typically done first with mediastinoscopy reserved for cases of negative EBUS results with persistent clinical concern for nodal involvement. The lymph nodes targeted should be those that will give the highest potential stage.⁸ Despite the excellent sensitivity of PET scan, endosonographic staging

studies have generally shown false negative rates for mediastinal disease of 5-10%. In one prospective trial of 35 non-small cell patients who underwent PET and EBUS, 10 had discordant results (histologic sampling down-staged six patients and upstaged four).⁹ This study underscores the importance of histologic confirmation, as PET imaging also may demonstrate false positive findings in setting of active infections or noninfectious inflammatory conditions such as sarcoidosis.

With the growing use of molecularly targeted therapies, acquisition of sufficient cytologic or pathologic material to perform such studies has become critically important. EBUS has been shown to provide adequate tissue, especially when guided by rapid on-site cytologic evaluation (ROSE).¹⁰ A broad array of needle sizes are now available, and studies have shown that EBUS-guided transbronchial needle aspiration (TBNA) can provide abundant material for a cell block which is subsequently sectioned for indicated studies.^{10,11} Immunohistochemical studies remain important to the initial diagnosis and protein expression studies, but next generation sequencing (NGS) platforms promise to continue to revolutionize the diagnosis of driver mutation oncogenes.

TRADITIONAL TREATMENT

Treatment has traditionally consisted of a combination of chemotherapy, radiation, and/or surgery depending on disease stage and patient factors (age, co-morbidities) (Table 1).¹²

Table 1. Treatment Options for Lung Cancer in 2004.

Stage	Primary Treatment	Adjuvant Therapy	5 Year Survival Rate
NSCLC Stage I	Surgical Resection	Chemotherapy	>60–70%
NSCLC Stage II	Surgical Resection	Chemotherapy with or without Radiotherapy	>40–50%
NSCLC Stage IIIA (Resectable)	Preoperative chemotherapy followed by surgical resection or surgical resection	Radiotherapy with chemotherapy or without chemotherapy	15–30%
NSCLC Stage IIIA (Unresectable) or IIIB (Contralateral or supraclavicular lymph nodes)	Chemotherapy and Radiation either concurrent or sequentially	None	10–20%
NSCLC Stage IIIB (pleural effusion) or Stage IV	Chemotherapy	None	10–15%
SCLC Limited Disease	Chemotherapy with radiation therapy	None	15–25%
SCLC Extensive Disease	Chemotherapy	None	<5%

Adapted from Spira A and Ettinger DS. Multidisciplinary management of lung cancer.¹²

MODERN ERA

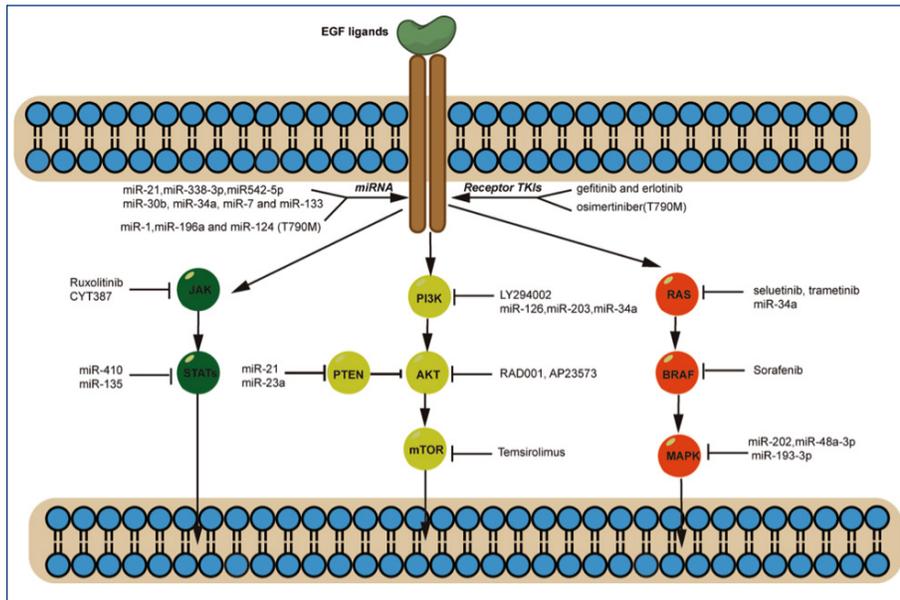
Since the early 2000s, the field has been revolutionized by the development and refinement of therapies in the areas of driver-mutation targeting, anti-angiogenesis, and immunotherapy. In particular, standard-of-care evaluation of newly diagnosed advanced NSCLC (particularly nonsquamous histologies) involves testing for at least the most common driver mutations with available therapies, as well as the PD-L1 protein expression as measured by the Tumor Proportion Score (TPS). The explosion in biomarker testing performed at one institution since 2004 can be seen in Figure 1 in the article by VanderLaan PA, et al¹³ at: <https://pubmed.ncbi.nlm.nih.gov/29413057/>.

EPIDERMAL GROWTH FACTOR (EGFR)

The epidermal growth factor receptor is a tyrosine kinase receptor and member of the Human Epidermal Receptor (HER) family. Binding of this transmembrane protein leads to downstream signal transduction pathways that drive tumor growth. The first study to enroll NSCLC patients in treatment with an EGFR inhibitor began patient enrollment in 1998. The landmark I-PASS study later randomized over 1200 patients in East Asia with pulmonary adenocarcinoma to gefitinib or carboplatin with paclitaxel and showed significant progression-free survival in the gefitinib treated group who harbored an EGFR mutation.¹⁴ While first well recognized in Asian populations (particularly never smoking young women), it is now recognized that 10-17% of patients with bronchogenic adenocarcinoma in the United States harbor an EGFR driver mutation.¹⁵ Oral EGFR inhibition in treatment of advanced nonsurgical disease has evolved from second-line or maintenance therapy after chemotherapy through to first-line treatment.¹⁶

Treated EGFR mutant NSCLC typically develop resistance to earlier generation EGFR inhibitors at approximately 10 months. Most of these patients develop an EGFR T790M mutation for which third-generation inhibitors were developed.¹⁵ Osimertinib is the prototypical third-generation therapy and has become the standard of care in EGFR mutant NSCLC due to improved systemic and central nervous system (CNS) control, as well as favorable side effect profile compared to earlier agents. The AURA3 study compared osimertinib to standard platinum therapy plus pemetrexed in patients previously treated with an earlier generation EGFR inhibitor and showed improved efficacy and side effect profile.¹⁶ Osimertinib has also recently shown improved progression-free survival of 19 months vs 10 months versus first-generation therapies in the FLAURA trial.¹⁷ Even more recently, the ADAURA study demonstrated that adjuvant osimertinib in surgically resected disease can have significant impact on disease-free survival (DFS).¹⁸ However, controversy exists as to its role in the adjuvant setting at this time, given the uncertainty as to whether routine adjuvant

Figure 2. Current pathways from the EGFR protein and the respective molecular targets, either FDA-approved or in clinical trials.



From Yuan, et al. The emerging treatment landscape of targeted therapy in non-small-cell lung cancer.¹⁹

use would provide true benefit over initiation at disease recurrence in carefully monitored patients and the present lack of overall survival data.

Overall, EGFR driver mutation investigation and development of therapies to evade resistance have represented a landmark strategy and paradigm shift for targeted therapies going forward.¹⁹ **Figure 2** presents a graphical representation of the EGF Receptor along with existing or potential targeted therapies against the receptor or its downstream effector pathways.

ANAPLASTIC LYMPHOMA KINASE

The anaplastic lymphoma kinase (ALK) gene is located on chromosome 2 and encodes a tyrosine kinase that is normally found at low levels in the small intestine, nervous system, and testis in adults. Activating alterations render the gene constitutively active. ALK-EML4 represents a rearrangement thus far only identified in NSCLC. ALK driver mutations are found in 5% of NSCLC.²⁰ Trials testing the first ALK inhibitor (crizotinib) began only three years after the recognition of ALK-positive NSCLC.²¹ Analogous to the evolution in EGFR inhibitors, ALK inhibition has improved with the newer agent alectinib showing a higher proportion of patients achieving overall response, improved CNS disease control, and better side-effect profile than crizotinib.²² ALK can also form a fusion protein with other druggable oncogenes, including c-ros oncogene (ROS1) and mesenchymal-epithelial transition factor (MET). In terms of relevance to clinical practice, NSCLC with ROS1 mutations is responsive to ALK inhibitors.²³

OTHER MOLECULARLY TARGETED THERAPIES

Since the seminal research on mutant EGFR and ALK targeting, many additional molecular targets have been identified including mutations within BRAF, RET, and NTRK genes. These are found commonly in nonsmokers with newly diagnosed NSCLC and occur in a smaller proportion of patients compared to EGFR mutations. Driver mutations in MET occur in about 3–4% of NSCLC patients and, in contrast to EGFR and ALK, are more commonly seen in patients over 70.²⁴ KRAS is the most common driver mutation found in smoking-induced NSCLC, but targeted treatment had remained elusive until sotorasib, which was granted accelerated approval by the FDA in May 2021. This targets the G12C mutation, which is present in approximately 13% of all NSCLC.²⁵ In a recent Phase II trial from 2021, partial or complete remission was seen in 37.1% of the patients. The median progression-free survival was 6.8 months, and the median duration of response was 11.1 months.

ANGIOGENESIS INHIBITION

In 2007, Sandler et al. published a landmark randomized control trial of the addition of the angiogenesis inhibitor bevacizumab to standard platinum-based therapy in the treatment of advanced (IIIB, IV) nonsquamous NSCLC. Median survival increased modestly from approximately ten to twelve months, but this was one of the first studies to show a survival advantage in advanced NSCLC with the addition of a novel/nonchemotherapy-based medication. Importantly, five patients in the bevacizumab treated group died of pulmonary hemorrhage, foreshadowing the era of novel treatment related adverse effects.²⁶ While angiogenesis inhibition has not shown robust benefit as the sole strategy in treatment of NSCLC, dual EGFR-VEGF pathway inhibition has shown significant promise, likely due to cross-talk and inhibition between these pathways.²⁷

IMMUNOTHERAPY

Immunotherapeutic approaches in cancer treatment are not new, as Interleukin-2 was an established yet radical treatment in attempts to cure renal cell carcinoma.²⁸ Increased recognition of the importance of the tumor microenvironment in the pathophysiology of malignant tumors led to efforts to utilize T-cell responses in antineoplastic therapy.

T-cells express the Programmed Cell Death-1 (PD-1) receptor while its ligand, PD-L1, is expressed on the surface of tumor cells or other cells in the tumor microenvironment. T-cells initially mount cytotoxic efforts towards neoplastic cells but the PD-L1/PD-1 interaction downregulates this response.²⁹

Not all tumors express high levels of PD-L1. The tumor proportion score (TPS) is an immunohistochemical score of the percentage of viable cells expressing PD-L1 and has been used as a biomarker to select patients for clinical trials. Tumor heterogeneity may negatively impact small biopsy or cytologic specimens' abilities to provide a score representative of the tumor overall, and some studies have shown clinical benefit with immunotherapy regardless of PD-L1 expression.^{30,31} Besides reflecting heterogeneity in tumor expression, this finding may also demonstrate the complexity of molecular pathways including T-cell/tumor interactions in the tumor microenvironment.

Initial studies demonstrating significant treatment effect utilizing immunotherapy in advanced malignancies not harboring a druggable oncogene (including NSCLC) were published in 2015. This led to the October 2015 FDA approval of pembrolizumab for advanced PD-L1 positive NSCLC that had progressed after other treatments.^{30,31} Since that time, immunotherapy has revolutionized the approach to treatment of most solid-organ malignancies. In 2017, the placebo-controlled PACIFIC trial published results of consolidative durvalumab in unresectable stage III patients who did not have disease progression on concurrent chemoradiotherapy. There were demonstrated improvements in the primary end points of progression-free survival and overall survival.³² These trials set the foundation for immunotherapy to completely change the treatment paradigm in stage IV and unresectable stage III disease.

Combination immunotherapeutic approaches utilizing inhibitors to the Cytotoxic T-lymphocyte Associated Antigen 4 (CTLA-4), such as ipilimumab with PD-L1 inhibitors, have been used extensively in treatment of metastatic melanoma and studied in NSCLC. Additional novel immunotherapeutic agents also hold substantial promise in NSCLC. Tiragolumab targets the immunomodulatory receptor TIGIT, which is a novel inhibitory immune checkpoint present on activated T-cells and NK cells. The CITYSCAPE trial is a phase II randomized trial that compared tiragolumab with atezolizumab versus atezolizumab alone in chemotherapy naive patients with high PD-L1 expression who did not have EGRF or ALK mutations. The treatment group showed improvement in overall response rate at 6 months (37% versus 21%) and a 42% reduction in the risk of disease as compared to the control arm.³³ This led to the approval of tiragolumab in conjunction with atezolizumab for NSCLC.

The burgeoning use of immunotherapy has led to increased recognition of immunotherapy-induced adverse events, which primarily take the form of autoimmune phenomenon.

These complications have, in turn, their own important diagnostic and treatment considerations. Any organ system can be involved but dermatologic, gastrointestinal, hepatic, and endocrine systems are the most encountered. Use in patients with significant pre-existing autoimmune conditions or interstitial lung disease represents at least a relative contraindication.

Of the various immune-related adverse effects, respiratory complications are associated with the highest morbidity and mortality. Pneumonitis has an incidence rate of approximately 5%, and patients typically present with cough and dyspnea. Milder cases often improve with medication cessation, but those with higher-grade disease need glucocorticoid therapy. Refractory cases or severe disease are often co-treated with steroid sparing agents.³⁴ Empiric therapy is usually used without biopsy of affected tissue, though the emergence of the novel coronavirus complicated this decision in some patients due to overlap in patterns of chest imaging abnormalities. Patients receiving concomitant chemotherapy can also pose a more difficult diagnostic dilemma as they can remain at risk of a broad array of opportunistic infections and drug-induced complications. The CTLA4 inhibitors have been associated with the development of mediastinal and hilar lymphadenopathy, with EBUS FNA often demonstrating noncaseating granulomatous inflammation indistinguishable from sarcoidosis.³⁵

LIQUID BIOPSY

Given the known predilection for malignant involvement of the peripheral circulation, there has been an increasing desire to capture diagnostic and molecular data from peripheral blood. The first FDA approval of a "liquid biopsy" test occurred in 2016 with approval of a cell free DNA (cfDNA) test to identify candidates for erlotinib based on exon 19 deletions or exon 21 (L858R) mutations in EGFR. Such testing has become routine in testing for mutations in druggable oncogenes. Besides cfDNA, currently available specimens include circulating tumor DNA (ctDNA), Circulating Tumor Cells (CTC), microRNA, exosomes, and tumor-educated platelets.³⁶ These "liquid biopsies" hold tantalizing promise in lung cancer due to ease of acquisition coupled with the explosion in information obtainable from next generation sequencing platforms. This data will likely guide stages from asymptomatic screening to adjuvant treatment and through to early detection of relapse, monitoring of treatment response and resistance testing.³⁷

The International Association for the Study of Lung Cancer (IASLC) recently released an updated consensus statement on the use of liquid biopsy techniques. Amongst other recommendations, the IASLC recommended use of NGS platforms rather than PCR-based technologies for determination of oncogene targets. The statement also highlights the paradigm shift away from tissue biopsy data as

the incontrovertible “gold standard” with realization that complementary genomic information can be obtained from plasma ctDNA analysis to inform druggable oncogene treatment. From a practical standpoint, for patients experiencing disease progression despite initial therapy, liquid biopsy techniques may represent the only feasible or safely accessible repository of tumor genomic data.³⁸

Recognizing the value of liquid biopsies, the FDA recently published a guideline for clinical trials conducted as part of the drug approval process (Figure 3). The proposal regarding potential trial designs incorporates liquid biopsy information to stratify patients at multiple points throughout the trial.³⁹

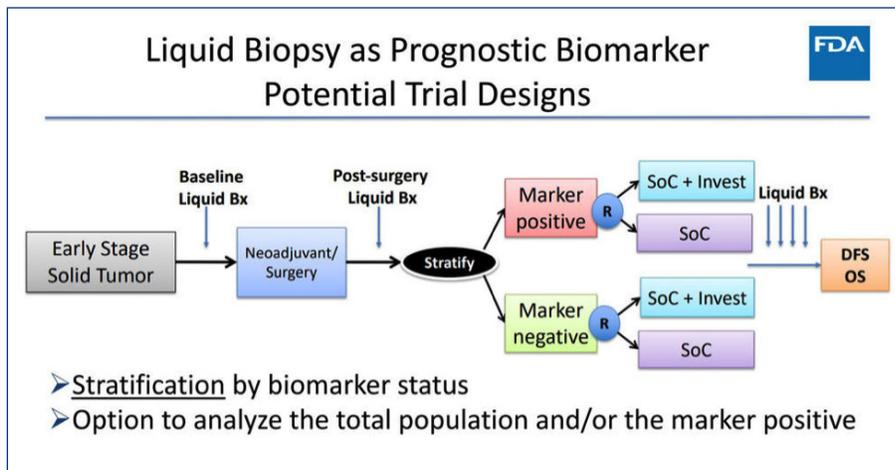
CONCLUSION

Over the past 15 years, there has been enormous progress in translating patient-specific cancer cell data into more effective treatment strategies in non-small-cell lung cancer, and this should only accelerate. Diagnostic strategies incorporating “liquid biopsies” will assuredly become more refined and important in the management of patients. Therapeutic approaches utilizing immunotherapy along with agents targeting druggable oncogenes and angiogenesis inhibitors as well as novel agents will continue. These novel therapies have unique side effect and adverse effect profiles in contrast to standard chemotherapeutics. An early referral to a pulmonologist can help facilitate the workup of pulmonary nodules since staging and adequate tissue sampling to assess these mutations are key to improving outcomes in NSCLC.

References

1. Center for Disease Control and Prevention. U.S. Cancer Statistics Lung Cancer. <https://www.cdc.gov/cancer/uscs/about/stat-bites/stat-bite-lung.htm>. Accessed June 8, 2021.
2. Siegel RL, Miller KD, Jemal A. Cancer Statistics, 2018. *CA: A Cancer Journal for Clinicians*. 2018; 68:7-30. doi:10.3322/caac.21442.
3. Lung-RADS Assessment Categories, Version 1.0. American College of Radiology. Lung CT Screening Reporting and Data System (Lung-RADSTM).
4. MacMahon H., Naidich D.P., Goo J.M., et. al. Guidelines for management of incidental pulmonary nodules detected on CT images: from the Fleischner Society 2017. *Radiology* 2017; 284: pp. 228-243.
5. Lababede O, Meziane MA. The Eighth Edition of TNM Staging of Lung Cancer: Reference Chart and Diagrams. *Oncologist*. 2018;23(7):844-848. doi:10.1634/theoncologist.2017-0659.
6. Chandrika S, Yarmus L. Recent Developments in Advanced Diagnostic Bronchoscopy. *European Respiratory Reviews*. 2020; 29: 190184. DOI: 10.1183/16000617.0184-2019.

Figure 3. FDA Perspectives on the use of liquid biopsies in NSCLC trial designs.



SoC = Standard of Care, DFS = Disease Free Survival, OS = Overall Survival

7. Um SW, Kim HK, Jung SH, Han J, Lee KJ, Park HY, Choi YS, Shim YM, Ahn MJ, Park K, Ahn YC, Choi JY, Lee KS, Suh GY, Chung MP, Kwon OJ, Kim J, Kim H. Endobronchial ultrasound versus mediastinoscopy for mediastinal nodal staging of non-small-cell lung cancer. *J Thorac Oncol* 2015; 10: pp. 331-337.
8. Rivera M.P., Mehta A.C., Wahidi M.M. Establishing the diagnosis of lung cancer: diagnosis and management of lung cancer, 3rd ed: American College of Chest Physicians evidence-based clinical practice guidelines. *Chest* 2013; 143: pp. e142S-e165S.
9. Steinfurt DP, Siva S, Leong TL, et al. Systematic Endobronchial Ultrasound-guided Mediastinal Staging Versus Positron Emission Tomography for Comprehensive Mediastinal Staging in NSCLC Before Radical Radiotherapy of Non-small Cell Lung Cancer: A Pilot Study. *Medicine (Baltimore)*. 2016;95(8):e2488. doi:10.1097/MD.0000000000002488
10. Cicek T, Ozturk A, Yilmaz A, Aktas Z, Demirag F, Akyurek N. Adequacy of EBUS-TBNA specimen for mutation analysis of lung cancer. *Clin Respir J*. 2019 Feb;13(2):92-97. doi: 10.1111/crj.12985. PMID: 30582673.
11. Wahidi, Momen M. MD, MBA*; Davidson, Kevin MD+; Shofer, Scott MD, PhD*; Mahmood, Kamran MD, MPH*; Cheng, George MD, PhD*; Giovacchini, Coral MD*; Jones, Claudia MD+; Jug, Rachel MB, BCh, BAO+; Pavlisko, Elizabeth N. MD+; Wang, Xiaofei PhD§; Gu, Lin MSS§; Weimholt, Cody DO; Zhou, Zhongren MD; Chen, Alexander MD. Pilot Study of the Performance of 19-G Needle in Endobronchial Ultrasound-guided Transbronchial Aspiration for the Diagnosis and Testing of Molecular Markers in Lung Cancer. *Journal of Bronchology & Interventional Pulmonology*: July 2021 - Volume 28 - Issue 3 - p 209-214 doi: 10.1097/LBR.0000000000000736
12. Spira A, Ettinger DS. Multidisciplinary management of lung cancer. *N Engl J Med*. 2004 Jan 22;350(4):379-92. doi: 10.1056/NEJMra035536. Erratum in: *N Engl J Med*. 2009 Apr 30;360(18):1917. PMID: 14736930.
13. VanderLaan PA, Rangachari D, Majid A, Parikh MS, Gangadharan SP, Kent MS, McDonald DC, Huberman MS, Kobayashi SS, Costa DB. Tumor biomarker testing in non-small-cell lung cancer: A decade of change. *Lung Cancer*. 2018 Feb;116:90-95. doi: 10.1016/j.lungcan.2018.01.002. Epub 2018 Jan 4. PMID: 29413057; PMCID: PMC5806129.
14. Mok T.S., Wu Y.L., Thongprasert S., et al. Gefitinib or carboplatin-paclitaxel in pulmonary adenocarcinoma. *N Engl J Med*. 2009; 361: 947-957.
15. Sullivan I, Planchard D. Osimertinib in the treatment of patients with epidermal growth factor receptor T790M mutation-positive metastatic non-small cell lung cancer: clinical trial evidence and experience. *Ther Adv Respir Dis*. 2016;10(6):549-565.
16. Mok TS, Wu Y-L, Ahn M-J, Garassino MC, Kim HR, Ramalingam SS, Shepherd FA, He Y, Akamatsu H, Theelen WS, Lee CK, Sebastian M, Templeton A, Mann H, Marotti M, Ghiorghiu S, Papadimitrakopoulou VA, AURA3 Investigators. Osimertinib

- or Platinum-Pemetrexid in EGFR T790M-Positive Lung Cancer. *N Engl J Med*. 2017 Feb 16;376(7):629-640. doi: 10.1056/NEJMoa1612674. Epub 2016 Dec 6. PMID: 27959700; PMCID: PMC6762027. doi:10.1177/1753465816670498
17. Soria JC, Ohe Y, Vansteenkiste J, Reungwetwattana T, Chewaskulyong B, Lee KH, Dechaphunkul A, Imamura F, Nogami N, Kurata T, Okamoto I, Zhou C, Cho BC, Cheng Y, Cho EK, Voon PJ, Planchard D, Su WC, Gray JE, Lee SM, Hodge R, Marrotti M, Rukazenkov Y, Ramalingam SS; FLAURA Investigators. Osimertinib in Untreated EGFR-Mutated Advanced Non-Small-Cell Lung Cancer. *N Engl J Med*. 2018 Jan 11;378(2):113-125. doi: 10.1056/NEJMoa1713137. Epub 2017 Nov 18. PMID: 29151359.
 18. Wu YL, Tsuboi M, He J, John T, Grohe C, Majem M, Goldman JW, Laktionov K, Kim SW, Kato T, Vu HV, Lu S, Lee KY, Akevanlop C, Yu CJ, de Marinis F, Bonanno L, Domine M, Shepherd FA, Zeng L, Hodge R, Atasoy A, Rukazenkov Y, Herbst RS; ADAURA Investigators. Osimertinib in Resected EGFR-Mutated Non-Small-Cell Lung Cancer. *N Engl J Med*. 2020 Oct 29;383(18):1711-1723. doi: 10.1056/NEJMoa2027071. Epub 2020 Sep 19. PMID: 32955177.
 19. Yuan M, Huang LL, Chen JH, et al. The emerging treatment landscape of targeted therapy in non-small-cell lung cancer. *Sig Transduct Target Ther* 4, 61 (2019). <https://doi.org/10.1038/s41392-019-0099-9>
 20. Sasaki T, Rodig SJ, Chirieac LR, Jänne PA. The biology and treatment of EML4-ALK non-small cell lung cancer. *Eur J Cancer*. 2010;46(10):1773-1780. doi:10.1016/j.ejca.2010.04.002
 21. Solomon BJ, Mok T, Kim D-W, Wu Y-L, Nakagawa K, Mekhail T, Felip E, Cappuzzo F, Paolini J, Usari T, et al. First-line crizotinib versus chemotherapy in ALK-positive lung cancer. *N. Engl. J. Med*. 2014;371:2167-2177. doi: 10.1056/NEJMoa1408440.
 22. Camidge DR, Dziadziuszko R, Peters S, Mok T, Noe J, Nowicka M, Gadgeel SM, Cheema P, Pavlakis N, de Marinis F, Cho BC, Zhang L, Moro-Sibilot D, Liu T, Bordogna W, Balas B, Muller B, Shaw AT. (2019) Updated efficacy and safety data and impact of the EML4-ALK fusion variant on the efficacy of alectinib in untreated ALK-positive advanced non-small cell lung cancer in the global phase III ALEX Study. *J Thorac Oncol* 14(7):1233-1243.
 23. Tang Z, Zhang J, Lu X, et al. Coexistent genetic alterations involving ALK, RET, ROS1 or MET in 15 cases of lung adenocarcinoma. *Mod Pathol* 31, 307-312 (2018). <https://doi.org/10.1038/modpathol.2017.109>
 24. Majeed U, Manochakian R, Zhao Y, Lou Y. Targeted therapy in advanced non-small cell lung cancer: current advances and future trends. *J Hematal Oncol*. 2021;14(1):108. Published 2021 Jul 8. doi:10.1186/s13045-021-01121-2
 25. Skoulidis F, Li BT, Dy GK, Price TJ, Falchook GS, Wolf J, et al. Sotorasib for lung cancers with KRAS p.G12C mutation. *N Engl J Med*. 2021; 384:2371-2381.
 26. Sandler A, Gray R, Perry MC, Brahmer J, Schiller JH, Dowlati A, Lilenbaum R, Johnson DH. Paclitaxel-carboplatin alone or with bevacizumab for non-small-cell lung cancer. *N Engl J Med*. 2006 Dec 14;355(24):2542-50. doi: 10.1056/NEJMoa061884. Erratum in: *N Engl J Med*. 2007 Jan 18;356(3):318. PMID: 17167137.
 27. Le X, Nilsson M, Goldman J, Reck M, Nakagawa K, Kato T, Ares LP, Frimodt-Moller B, Wolff K, Visseren-Grul C, Heymach JV, Garon EB. Dual EGFR-VEGF Pathway Inhibition: A Promising Strategy for Patients With EGFR-Mutant NSCLC. *J Thorac Oncol*. 2021 Feb;16(2):205-215. doi: 10.1016/j.jtho.2020.10.006. Epub 2020 Oct 20. PMID: 33096270.
 28. Rosenberg SA, Yang JC, Topalian SL, Schwartzentruber DJ, Weber JS, Parkinson DR, Seipp CA, Einhorn JH, White DE. Treatment of 283 consecutive patients with metastatic melanoma or renal cell cancer using high-dose bolus interleukin 2. *JAMA*. 1994 Mar 23-30;271(12):907-13. PMID: 8120958.
 29. Francisco LM, Salinas VH, Brown KE, Vanguri VK, Freeman GJ, Kuchroo VK, Sharpe AH. PD-L1 regulates the development, maintenance, and function of induced regulatory T cells. *J Exp Med*. 2009 Dec 21;206(13):3015-29. doi: 10.1084/jem.20090847. Epub 2009 Dec 14. PMID: 20008522; PMCID: PMC2806460.
 30. Reck M, Rodríguez-Abreu D, Robinson AG, Hui R, Csőszi T, Fülöp A, Gottfried M, Peled N, Tafreshi A, Cuffe S, O'Brien M, Rao S, Hotta K, Leiby MA, Lubiniecki GM, Shentu Y, Rangwala R, Brahmer JR; KEYNOTE-024 Investigators. Pembrolizumab versus Chemotherapy for PD-L1-Positive Non-Small-Cell Lung Cancer. *N Engl J Med*. 2016 Nov 10;375(19):1823-1833. doi: 10.1056/NEJMoa1606774. Epub 2016 Oct 8. PMID: 27718847.
 31. Gandhi L, Rodríguez-Abreu D, Gadgeel S, Esteban E, Felip E, De Angelis F, Domine M, Clingan P, Hochmair MJ, Powell SF, Cheng SY, Bischoff HG, Peled N, Grossi F, Jennens RR, Reck M, Hui R, Garon EB, Boyer M, Rubio-Viqueira B, Novello S, Kurata T, Gray JE, Vida J, Wei Z, Yang J, Raftopoulos H, Pietanza MC, Garassino MC; KEYNOTE-189 Investigators. Pembrolizumab plus Chemotherapy in Metastatic Non-Small-Cell Lung Cancer. *N Engl J Med*. 2018 May 31;378(22):2078-2092. doi: 10.1056/NEJMoa1801005. Epub 2018 Apr 16. PMID: 29658856.
 32. Gray JE, Villegas A, Daniel D, Vicente D, Murakami S, Hui R, Kurata T, Chiappori A, Lee KH, Cho BC, Planchard D, Paz-Ares L, Favier-Finn C, Vansteenkiste JF, Spigel DR, Wadsworth C, Taboada M, Dennis PA, Özgüroğlu M, Antonia SJ. Three-Year Overall Survival with Durvalumab after Chemoradiotherapy in Stage III NSCLC-Update from PACIFIC. *J Thorac Oncol*. 2020 Feb;15(2):288-293. doi: 10.1016/j.jtho.2019.10.002. Epub 2019 Oct 14. PMID: 31622733; PMCID: PMC7244187.
 33. Rodríguez-Abreu D et al. CITYSCAPE: Primary Analysis of a Randomized, Double-Blind, Phase II Study of the Anti-TIGIT Antibody Tiragolumab plus Atezolizumab versus Placebo plus Atezolizumab as 1L Treatment in Patients with PD-L1-Selected NSCLC. Presented at: ASCO 2020 Virtual Scientific Program; 2020 May 29-31.
 34. Naidoo J, Wang X, Woo KM, Iyriboz T, Halpenny D, Cunningham J, Chaff JE, Segal NH, Callahan MK, Lesokhin AM, Rosenberg J, Voss MH, Rudin CM, Rizvi H, Hou X, Rodriguez K, Albano M, Gordon RA, Leduc C, Rektman N, Harris B, Menzies AM, Guminski AD, Carlino MS, Kong BY, Wolchok JD, Postow MA, Long GV, Hellmann MD. Pneumonitis in Patients Treated With Anti-Programmed Death-1/Programmed Death Ligand 1 Therapy. *J Clin Oncol*. 2017 Mar;35(7):709-717. doi: 10.1200/JCO.2016.68.2005. Epub 2016 Sep 30. Erratum in: *J Clin Oncol*. 2017 Aug 1;35(22):2590. PMID: 27646942; PMCID: PMC5559901.
 35. Tetzlaff MT, Nelson KC, Diab A, et al. Granulomatous/sarcoid-like lesions associated with checkpoint inhibitors: a marker of therapy response in a subset of melanoma patients. *J Immunother Cancer*. 2018;6(1):14. Published 2018 Feb 12. doi:10.1186/s40425-018-0323-0
 36. Freitas C, Sousa C, Machado F, et al. The Role of Liquid Biopsy in Early Diagnosis of Lung Cancer. *Front Oncol*. 2021;11:634316. Published 2021 Apr 16. doi:10.3389/fonc.2021.634316
 37. Guibert N, Pradines A, Favre G, Mazieres J. Current and future applications of liquid biopsy in nonsmall cell lung cancer from early to advanced stages. *Eur Respir Rev*. 2020 Feb 12;29(155):190052. doi: 10.1183/16000617.0052-2019. PMID: 32051167.
 38. Rolfo C, Mack P, Scagliotti GV, Aggarwal C, Arcila ME, Barlesi F, Bivona T, Diehn M, Dive C, Dziadziuszko R, Leigh N, Malapelle U, Mok T, Peled N, Raez LE, Sequist L, Sholl L, Swanton C, Abbosch C, Tan D, Wakelee H, Wistuba I, Bunn R, Freeman-Daily J, Wynes M, Belani C, Mitsudomi T, Gandara D. Liquid Biopsy for Advanced Non-Small Cell Lung Cancer: A Consensus Statement from The International Association for the Study of Lung Cancer (IASLC). *J Thorac Oncol*. 2021 Jul 8;S1556-0864(21)02284-X. doi: 10.1016/j.jtho.2021.06.017. Epub ahead of print. PMID: 34246791.
 39. Nyberg, Kara, et al. "FDA Perspectives on the Use of LIQUID Biopsy in NSCLC." IASLC, 30 July 2021, www.iaslc.org/iaslc-news/ilcn/fda-perspectives-use-liquid-biopsy-nsclc.

Authors

Daniel Dustin, DO, Division of Pulmonary, Critical Care and Sleep Medicine, Warren Alpert Medical School of Brown University, Providence, RI.

Douglas Martin, MD, Division of Pulmonary, Critical Care and Sleep Medicine, Warren Alpert Medical School of Brown University, Providence, RI.

Correspondence

Douglas Martin, MD

Division of Pulmonary Critical Care and Sleep Medicine

593 Eddy Street

Providence, Rhode Island 02903