THE NEXT LEVEL in PULMONARY CARE: What YOU Need to Know in 2019

INTERSTITIAL LUNG DISEASE • ASTHMA • COPD • PH

NATIONAL EDUCATION SERIES
Overarching Principles
IPF ◆ Pulmonary Hypertension ◆ Asthma ◆ COPD

• Patient education regarding their illness and appropriate treatment expectations
• Patients are partners in therapy
• Importance of multidisciplinary teams
<table>
<thead>
<tr>
<th>Category</th>
<th>Diseases</th>
<th>Sub-categories/examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Idiopathic</td>
<td><strong>Idiopathic Interstitial Pneumonias (IIPs)</strong></td>
<td>IPF, NSIP, Unclassifiable, COP, RB-ILD, DIP, AIP, LIP, PPFE</td>
</tr>
<tr>
<td></td>
<td>Sarcoidosis</td>
<td></td>
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<td></td>
<td>Amyloidosis</td>
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<tr>
<td></td>
<td>Lymphangioleiomyomatosis</td>
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<tr>
<td></td>
<td>PLCH, Eosinophilic pneumonia. Neurofibromatosis, DAH</td>
<td></td>
</tr>
<tr>
<td>Immunologic</td>
<td>Connective tissue disorders</td>
<td></td>
</tr>
<tr>
<td>Inhalational</td>
<td>Inorganic</td>
<td>Asbestosis, silicosis</td>
</tr>
<tr>
<td></td>
<td>Organic: Chronic hypersensitivity pneumonitis</td>
<td>Bird fanciers disease, farmer’s lung</td>
</tr>
<tr>
<td></td>
<td>Antiarrhythmics, antimicrobials, chemotherapy agents, biologics</td>
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<tr>
<td></td>
<td>Radiation</td>
<td></td>
</tr>
<tr>
<td>Iatrogenic</td>
<td>Viral</td>
<td>CMV, influenza</td>
</tr>
<tr>
<td></td>
<td>Fungal</td>
<td>Pneumocystis carinii</td>
</tr>
<tr>
<td>Infectious</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chronic CHF</td>
<td>Lymphangitic carcinomatosis</td>
<td></td>
</tr>
<tr>
<td>Neoplastic</td>
<td>Bronchoalveolar carcinoma</td>
<td></td>
</tr>
</tbody>
</table>

Fibrotic Lung Disease: Sorting Out the Alphabet Soup

Where does IPF fit in the context of the ILDs?

- IPF is the most common of the idiopathic interstitial pneumonias (IIPs)
- Definition of IPF:
  - Chronic, progressive fibrosing interstitial pneumonia of unknown cause
  - Older adults
  - Limited to the lungs
  - Histopathologic and/or radiologic pattern of UIP

Key Clinical Features of IPF

- Increasing breathlessness on exertion
- Non-productive cough
- Patient age > 50 years
- Bibasilar inspiratory crackles
- Digital clubbing in many cases

IPF Diagnosis: Flow Diagram-ATS Guidelines, 2018

HRCT is critical in the diagnostic process

Usual Interstitial Pneumonia (UIP) is the hallmark pattern of IPF

- Refined radiological AND histopathological patterns of UIP to 4 diagnostic categories
  - UIP
  - Probable UIP
  - Indeterminate
  - Alternate diagnosis

UIP Pattern on HRCT

- Subpleural reticulation
- Honeycomb cysts
- No atypical features

= UIP pattern
Making the Diagnosis of IPF: Placing HRCT in Context of Lung Biopsy

<table>
<thead>
<tr>
<th>IPF Suspected</th>
<th>Histopathology Pattern</th>
<th>Alternate Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>UIP</td>
<td>Probable UIP</td>
</tr>
<tr>
<td>HRCT Pattern</td>
<td></td>
<td></td>
</tr>
<tr>
<td>UIP</td>
<td>IPF</td>
<td>IPF</td>
</tr>
<tr>
<td>Probable UIP</td>
<td>IPF</td>
<td>IPF</td>
</tr>
<tr>
<td>Indeterminate</td>
<td>IPF</td>
<td>IPF (likely)</td>
</tr>
<tr>
<td>Alternate Diagnosis</td>
<td>IPF (likely)</td>
<td>Non-IPF dx</td>
</tr>
</tbody>
</table>

Threshold for IPF Diagnosis

"Clinomics"
- Increasing age
- No exposures
- No CTD
- ILD

"IPF-ometer"

HRCT
- Alternate diagnosis
- Indeterminate UIP pattern
- Probable UIP pattern
- UIP pattern

Concept slide (from the mind of a Bayesian)
ILD: Developing an Index of Suspicion for IPF vs. Other

• What is the pretest likelihood for IPF?
  – Depends on how old
  – Depends on exposure history
    • Smoking (increases likelihood of IPF)
    • Birds, molds (increases likelihood of Chronic HP)
  – Depends on gender
  – Depends on presence or absence of CTD features

• Exclusion of other known causes of ILD is important given differences in clinical course, management and outcomes
“Look, Listen and Walk”

• **LOOK** at the skin and fingers

• **LISTEN** carefully for crackles
  — Both lung bases
  — Laterally in mid-axillary line
  — Anteriorly

• **WALK** the patient in the hallway (or on a staircase)
  — Try to elicit exertional dyspnea if possible
  — Measure SpO$_2$ before and after walking
  — A 3% drop in SpO$_2$ indicates exertional desaturation
## Attempt to Identify the Cause of ILD

**Perform a Detailed History and Physical**

<table>
<thead>
<tr>
<th>Disease</th>
<th>Questions/Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug/Radiation-induced ILD</td>
<td>Chemotherapy, amiodarone, nitrofurantoin, other drugs; check PneumoTox.com, radiation therapy to the chest</td>
</tr>
<tr>
<td>Connective Tissue Disease-related ILD</td>
<td>Joints, skin, Raynaud’s reflex, dry eyes/mouth, muscle weakness or pain</td>
</tr>
<tr>
<td>Vasculitis</td>
<td>Sinus disease, hoarseness, hematuria, hemoptysis</td>
</tr>
<tr>
<td>Chronic Hypersensitivity Pneumonitis</td>
<td>Exposure to mold sources, birds, down bedding, farming or agriculture</td>
</tr>
<tr>
<td>Pneumoconioses</td>
<td>Occupational history</td>
</tr>
<tr>
<td>Familial ILD</td>
<td>Family history of ILD, sarcoidosis, home oxygen use, autoimmune disease</td>
</tr>
</tbody>
</table>

PFF Pocket Card, kindly provided by PFF
## Attempt to Identify the Cause of ILD Continued

### Order Relevant Blood Tests

<table>
<thead>
<tr>
<th>Disease</th>
<th>Blood Tests</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eosinophilic pneumonia</td>
<td>CBC with differential</td>
</tr>
<tr>
<td>Sarcoidosis</td>
<td>Serum calcium</td>
</tr>
<tr>
<td>Scleroderma/MCTD</td>
<td>ANA, Scl70, centromere, U1RNP</td>
</tr>
<tr>
<td>Rheumatoid arthritis</td>
<td>RF, CCP</td>
</tr>
<tr>
<td>Sjogren’s</td>
<td>ANA, Ro/SSA, La/SSB</td>
</tr>
<tr>
<td>Idiopathic inflammatory myositis</td>
<td>ANA, Jo-1, CK, myoglobin, aldolase, consider myositis panel</td>
</tr>
<tr>
<td>Vasculitis</td>
<td>Anti-PR3 and MPO (ANCA), creatinine</td>
</tr>
<tr>
<td>Chronic hypersensitivity pneumonitis</td>
<td>HP panel (controversial)</td>
</tr>
<tr>
<td>CTD-ILD</td>
<td>ESR, CRP</td>
</tr>
</tbody>
</table>

PFF Pocket Card, kindly provided by PFF
Impact of Multidisciplinary Team Discussion on IPF Diagnosis at Referral Center

*P < 0.05 using McNemar’s test

Referral diagnosis of IPF (n=27)

No change in diagnosis of IPF (n=17)

MDM diagnosis of IPF (n=25)

Management Recommendations

- Monitor
- Clinical trial
- Wean prednisone
- Oxygen
- Pulmonary vasodilators
- Antifibrotics
- Steroid sparing agents
- Steroids

Importance of Early Diagnosis and Referral

Delayed Access to Subspecialty Care and Survival

Survival

p for trend = 0.04

Management of Patients with IPF
IPF Has an Unpredictable Disease Course

Variable onset of symptoms

Unpredictable patterns of progression

Demise

Time

Disease Progression
IPF: Survival in the Pre-antifibrotic Era 2000-2009 (N=521)

Median survival: 36 and 42 months

Decline in FVC Associated with Decreased Probable Survival

Analysis of 1132 placebo-treated subjects from six studies of the clinical development for nintedanib and pirfenidone

Registry Data: The Impact of Antifibrotic Therapy on Survival

**Australia**

Transplant-free survival (%)

- No antifibotics (n=501)
- Antifibotics (n=146)

Time years

**Europe**

Kaplan Meier plot of cumulative survival

- antifibrotic treatment
- no antifibrotic treatment

Timespan (months) first diagnosis-last visit or death

$p = 0.001$


[www.PILOTforPulmonary.org](http://www.PILOTforPulmonary.org)
Approved Antifibrotic Therapies for Patients with IPF

**Pirfenidone**
- FDA approval 2014
- Anti-fibrotic properties; exact mechanism of action unknown
- Orally administered, 801 mg, three times daily
- Nausea, rash/sun sensitivity, dyspepsia/GERD

**Nintedanib**
- FDA approval 2014
- Tyrosine kinase inhibitor; targets FGFR, PDGFR, VEGFR, FLT3
- Orally administered, 150 mg, two times daily
- Diarrhea, nausea

Pirfenidone. [https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/022535s005lbl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/022535s005lbl.pdf)
Nintedanib. [https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/205832s004lbl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/205832s004lbl.pdf)
Pirfenidone: Significant Improvement in FVC Decline

Pirfenidone Associated with Reduction in Relative Risk of Mortality vs. Placebo (120 Weeks)

Nintedanib: Significant Improvement in FVC Decline

**INPULSIS-1**
- Nintedanib, 150 mg Twice Daily (N=309)
- Placebo (N=204)
- Adjusted Annual Rate of Change in FVC (ml/yr)
- Difference, 125.3 (95% CI, 77.7–172.8)
P<0.001
- 52% Relative Reduction

**INPULSIS-2**
- Nintedanib, 150 mg Twice Daily (N=329)
- Placebo (N=219)
- Adjusted Annual Rate of Change in FVC (ml/yr)
- Difference, 93.7 (95% CI, 44.8–142.7)
P<0.001
- 45% Relative Reduction

Mortality Data from TOMORROW and INPULSIS Trials (Nintedanib vs Placebo, 52 Weeks)

All-Cause Mortality
- Nintedanib (n = 723) 5.8%
- Placebo (n = 508) 3.5%
- HR = 0.70, 0.46-1.08
- P = 0.095

On-Treatment Mortality
- Nintedanib (n = 723) 3.5%
- Placebo (n = 508) 2%
- HR = 0.57, 0.34-0.97
- P = 0.027

Respiratory Mortality
- Nintedanib (n = 723) 8.3%
- Placebo (n = 508) 5.7%
- HR = 0.62, 0.37-1.06
- P = 0.078

Time to First Acute Exacerbation (Investigator-reported): INPULSIS Pooled

<table>
<thead>
<tr>
<th>Time to First Acute Exacerbation (days)</th>
<th>Nintedanib 150 mg bid (n=638)</th>
<th>Placebo (n=423)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cumulative incidence of first investigator-reported acute exacerbation (%)</td>
<td>0 1 2 3 4 5 6 7 8 9 10</td>
<td>0 1 2 3 4 5 6 7 8 9 10</td>
</tr>
</tbody>
</table>

HR 0.64  
(95% CI; 0.39, 1.05)  
\( P = .0823 \)

Patients with ≥1 acute exacerbation, n (%)  
<table>
<thead>
<tr>
<th>Nintedanib 150 mg bid</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>31 (4.9)</td>
<td>32 (7.6)</td>
</tr>
</tbody>
</table>
Does Disease Severity Matter?

Pirfenidone was associated with decreases in the proportion of patients experiencing categorical declines in the three outcomes, with no significant differences between mild and moderate disease.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Subgroup</th>
<th>Standardized treatment effect</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>FVC</td>
<td>FVC &lt;80%</td>
<td><img src="image" alt="graph" /></td>
<td>0.3969</td>
</tr>
<tr>
<td></td>
<td>FVC ≥80%</td>
<td><img src="image" alt="graph" /></td>
<td></td>
</tr>
<tr>
<td>6MWD</td>
<td>FVC &lt;80%</td>
<td><img src="image" alt="graph" /></td>
<td>0.9583</td>
</tr>
<tr>
<td></td>
<td>FVC ≥80%</td>
<td><img src="image" alt="graph" /></td>
<td></td>
</tr>
<tr>
<td>UCSD SOBQ</td>
<td>FVC &lt;80%</td>
<td><img src="image" alt="graph" /></td>
<td>0.1957</td>
</tr>
<tr>
<td></td>
<td>FVC ≥80%</td>
<td><img src="image" alt="graph" /></td>
<td></td>
</tr>
</tbody>
</table>

6-MWD, 6-minute walk distance; UCSD SOBQ, University of California San Diego Shortness of Breath Questionnaire

Consistent Effect of Nintedanib Across Patient Subgroups

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Placebo</th>
<th>Nintedanib 150 mg bid</th>
</tr>
</thead>
<tbody>
<tr>
<td>All</td>
<td>423</td>
<td>638</td>
</tr>
<tr>
<td>Male</td>
<td>334</td>
<td>507</td>
</tr>
<tr>
<td>Female</td>
<td>89</td>
<td>131</td>
</tr>
<tr>
<td>Age &lt;65 years</td>
<td>145</td>
<td>258</td>
</tr>
<tr>
<td>Age ≥65 years</td>
<td>278</td>
<td>380</td>
</tr>
<tr>
<td>White</td>
<td>248</td>
<td>360</td>
</tr>
<tr>
<td>Asian</td>
<td>128</td>
<td>194</td>
</tr>
<tr>
<td>FVC ≤70% predicted</td>
<td>154</td>
<td>207</td>
</tr>
<tr>
<td>FVC &gt;70% predicted</td>
<td>269</td>
<td>431</td>
</tr>
<tr>
<td>SGRQ total score ≤40</td>
<td>232</td>
<td>323</td>
</tr>
<tr>
<td>SGRQ total score &gt;40</td>
<td>187</td>
<td>301</td>
</tr>
<tr>
<td>Never smoked</td>
<td>122</td>
<td>174</td>
</tr>
<tr>
<td>Ex-/current smoker</td>
<td>301</td>
<td>464</td>
</tr>
<tr>
<td>Corticosteroids for systemic use</td>
<td>89</td>
<td>136</td>
</tr>
<tr>
<td>No corticosteroids for systemic use</td>
<td>334</td>
<td>502</td>
</tr>
<tr>
<td>Bronchodilator use</td>
<td>72</td>
<td>129</td>
</tr>
<tr>
<td>No bronchodilator use</td>
<td>351</td>
<td>509</td>
</tr>
</tbody>
</table>

Nintedanib vs placebo difference in adjusted rate of decline in FVC, mL/year (95% CI)

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>N analyzed</th>
<th>Difference</th>
<th>95% CI</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>All</td>
<td>423</td>
<td>109.9</td>
<td>(75.9, 144.0)</td>
<td>0.1911</td>
</tr>
<tr>
<td>Male</td>
<td>334</td>
<td>115.7</td>
<td>(75.5, 156.0)</td>
<td>0.3832</td>
</tr>
<tr>
<td>Female</td>
<td>89</td>
<td>90.7</td>
<td>(32.1, 149.2)</td>
<td>0.7184</td>
</tr>
<tr>
<td>Age &lt;65 years</td>
<td>145</td>
<td>115.2</td>
<td>(55.1, 175.2)</td>
<td></td>
</tr>
<tr>
<td>Age ≥65 years</td>
<td>278</td>
<td>105.9</td>
<td>(64.6, 147.3)</td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>248</td>
<td>123.4</td>
<td>(78.2, 168.6)</td>
<td></td>
</tr>
<tr>
<td>Asian</td>
<td>128</td>
<td>94.1</td>
<td>(33.7, 154.6)</td>
<td></td>
</tr>
<tr>
<td>FVC ≤70% predicted</td>
<td>154</td>
<td>113.5</td>
<td>(51.3, 175.7)</td>
<td>0.9505</td>
</tr>
<tr>
<td>FVC &gt;70% predicted</td>
<td>269</td>
<td>109.0</td>
<td>(68.2, 149.9)</td>
<td></td>
</tr>
<tr>
<td>SGRQ total score ≤40</td>
<td>232</td>
<td>100.6</td>
<td>(57.1, 144.0)</td>
<td></td>
</tr>
<tr>
<td>SGRQ total score &gt;40</td>
<td>187</td>
<td>125.0</td>
<td>(69.5, 180.6)</td>
<td></td>
</tr>
</tbody>
</table>

Nintedanib vs placebo difference in adjusted rate of decline in FVC in mL/year and 95% CI

Common Side Effects Associated with Antifibrotic Therapy in Patients with IPF

Retrospective chart review; N = 186
Temple Lung Center, Philadelphia PA

Engaging in a Shared Decision-Making Process

- Discuss the efficacy and safety of FDA-approved therapies
- Listen to the patient’s preferences and concerns
- Set treatment expectations
Engaging in a Shared Decision-Making Process

**Additionally:**
- Focus on symptom control and management of comorbidities
- Consider the option of lung transplantation
Pirfenidone and Nintedanib
Elevated Liver Enzymes and Monitoring

**Pirfenidone**
- ALT, AST and bilirubin elevations have occurred
- Monitor ALT, AST and bilirubin before treatment, then monthly for the first six months and every three months thereafter
- Temporary dosage reductions or discontinuations may be required

**Nintedanib**
- ALT, AST and bilirubin elevations have occurred, including cases of drug-induced liver injury
- Most hepatic events occur within the first three months of treatment
- Monitor ALT, AST and bilirubin prior to treatment, at regular intervals during the first three months, and periodically thereafter or as clinically indicated
- Temporary dosage reductions or discontinuations may be required

Pirfenidone. [https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/022535s005lbl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/022535s005lbl.pdf)
Nintedanib. [https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/205832s009lbl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/205832s009lbl.pdf)
Recommendations for Optimizing Treatment Adherence in Patients with IPF

• Establish clear treatment expectations
  – Drugs are unlikely to improve symptoms
  – Partner with patient to manage any side effects
  – Unable to distinguish if drug “is working”
• Discuss the importance of treatment adherence
• Monitor and manage treatment-related side effects
• Implement dose reduction protocols, as appropriate
• Consider treatment switch for intolerable side effects despite dose adjustments and other symptom management strategies
Monitoring for Disease Progression

• Consider every three months:
  – PFTs (at least FVC and DLCO)
  – 6-MWT (distance/nadir saturation)
  – $O_2$ requirement during activity
  – Comorbidities
  – Use of dyspnea and cough questionnaires
    • (UCSD, SGRQ, CQLQ, LCQ)
  – Assessment of overnight pulse oximetry to assess for nocturnal desaturation

• Repeat imaging:
  – Consider HRCT upon suspicion of clinical worsening
  – Consider CT angiogram if any suspicion for PE
At Each Visit

• Ask yourself and your patient:
  – Are we still comfortable with what we’re doing?
  – Assess quality of life, challenges
  – Side effects of medications
  – Should we change anything?
  – Are there data to support doing anything differently?

• Determine whether your patient is progressing
  – If unsure, bring him/her back in six weeks and obtain another data point
Comprehensive IPF Management

- Vaccinations
- Antifibrotic therapy (nintedanib or pirfenidone)
- Management of patients with IPF
- Supplemental oxygen
- Symptom management
- Pulmonary rehabilitation
- Consider lung transplant evaluation
- Palliative care
- Management of comorbidities
- Consider clinical trial participation

Patient education and support

Prevalence of IPF Comorbidities

- Obstructive sleep apnoea: 5-91%
- Depression or anxiety: 21-49%
- Gastro-oesophageal reflux disease: 0-94%
- Pulmonary embolism: 3-6%
- Pulmonary hypertension: 3-86%
- Congestive heart failure: 4-26%
- Chronic obstructive pulmonary disease: 6-67%
- Coronary artery disease: 3-68%
- Diabetes mellitus: 10-42%
- Lung cancer: 4-23%

Sarcopenia prevalence: poorly defined but common
<table>
<thead>
<tr>
<th>Comorbidity</th>
<th>Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pulmonary hypertension</td>
<td>Treatment has not been shown to be helpful; recommend vasodilator therapy only be used in RCTs or at expert centers</td>
</tr>
<tr>
<td>Combined pulmonary fibrosis and emphysema</td>
<td>Trial of bronchodilator therapy is reasonable; consider antifibrotic therapy</td>
</tr>
<tr>
<td>Lung cancer</td>
<td>Optimal treatment strategies are poorly defined; selected patients might be candidates for surgical resection</td>
</tr>
<tr>
<td>GERD</td>
<td>Mixed data regarding antacid therapy; recent trial of antireflux surgery</td>
</tr>
<tr>
<td>Cardiac disease</td>
<td>Consider ischemia assessment or CHF in differential diagnosis of dyspnea in patients with IPF; standard management strategies apply to persons with IPF</td>
</tr>
<tr>
<td>Venous thromboembolism</td>
<td>Anticoagulation should be prescribed when there is a clinical indication; optimal coagulant for IPF not yet determined</td>
</tr>
<tr>
<td>Depression and anxiety</td>
<td>Screen all patients with IPF for depression; treatment with antidepressants and counseling is reasonable</td>
</tr>
<tr>
<td>Deconditioning</td>
<td>Pulmonary rehabilitation improves functional status and QOL</td>
</tr>
<tr>
<td>Sleep-disordered breathing</td>
<td>Refer all patients with IPF for sleep study; treatment with CPAP with diagnosed with OSA</td>
</tr>
<tr>
<td>Diabetes</td>
<td>Effects of glycemic control on IPF progression unknown; standard diabetes management</td>
</tr>
</tbody>
</table>

Adapted from King T, Nathan S. Lancet Respir Med. 2017;5:72-84.
Selected Agents in Ongoing IPF/ILD Studies*

- Approved antifibrotics (pirfenidone, nintedanib) in ILDs other than IPF
- Pentraxin 2 (purified serum amyloid P): inhibits monocyte differentiation into profibrotic fibrocytes; also a potent inhibitor of monocyte differentiation into proinflammatory macrophages and production of TGF-β1
- Pamrevlumab: fully human monoclonal antibody that inhibits the activity of connective tissue growth factor, a critical mediator in the progression of fibrosis
- GLPG1690: autotaxin inhibitor
- Co-trimoxazole: antibiotic

*Not comprehensive list
Nintedanib Clinical Trials in ILDs

**Efficacy and Safety of Nintedanib in Patients With Progressive Fibrosing Interstitial Lung Disease (PF-ILD)**
- Double-blind, randomized, placebo-controlled phase 3 trial

**SENSCIS (Safety and Efficacy of Nintedanib in Systemic Sclerosis) Study**
- Double-blind, randomized, placebo-controlled phase 3 trial

**A Study of Nintedanib for Lymphangioleiomyomatosis (LAM)**
- Open label, phase 2 trial

[https://clinicaltrials.gov/ct2/show/NCT02999178](https://clinicaltrials.gov/ct2/show/NCT02999178)
[https://clinicaltrials.gov/ct2/show/NCT02597933](https://clinicaltrials.gov/ct2/show/NCT02597933)
[https://clinicaltrials.gov/ct2/show/NCT03062943](https://clinicaltrials.gov/ct2/show/NCT03062943)
Pirfenidone Clinical Trials in ILDs

Safety and Tolerability of Pirfenidone in Participants With Systemic Sclerosis–Related Interstitial Lung Disease (SSc-ILD) (LOTUSS)

- Open label, phase 2 trial is completed

Phase 2 Study of Pirfenidone in Patients With RA-ILD

- Randomized, placebo-controlled phase 2 study

Study of Efficacy and Safety of Pirfenidone in Patients With Fibrotic HP Study

- Randomized, placebo-controlled trial

A Study of Pirfenidone in Patients With Unclassifiable Progressive Fibrosing ILD

- Double-blind, randomized, placebo-controlled phase 2 trial

IPF Pearls

• For shortness of breath and/or chronic cough, think of less common causes when findings are not consistent with COPD, asthma, CHF, etc.

• Diagnosis of IPF
  – Rule out identifiable causes of ILD
  – UIP pattern on HRCT chest OR surgical lung biopsy (where applicable)

• Early diagnosis and referral are important for optimizing outcomes

• Nintedanib and pirfenidone have been shown to reduce decline in lung function in IPF

• Comprehensive management includes pharmacologic therapy, treatment of comorbidities, symptom relief and pulmonary rehabilitation

• Patient education is important for participation in shared decision-making in management of disease and treatment-related side effects
### Pulmonary Hypertension

**TABLE 1** Haemodynamic definitions of pulmonary hypertension (PH)

<table>
<thead>
<tr>
<th>Definitions</th>
<th>Characteristics</th>
<th>Clinical groups&lt;br&gt; #</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-capillary PH</td>
<td>mPAP &gt; 20 mmHg</td>
<td>1, 3, 4 and 5</td>
</tr>
<tr>
<td></td>
<td>PAWP ≤ 15 mmHg</td>
<td></td>
</tr>
<tr>
<td></td>
<td>PVR ≥ 3 WU</td>
<td></td>
</tr>
<tr>
<td>Isolated post-capillary PH (IpcPH)</td>
<td>mPAP &gt; 20 mmHg</td>
<td>2 and 5</td>
</tr>
<tr>
<td></td>
<td>PAWP &gt; 15 mmHg</td>
<td></td>
</tr>
<tr>
<td></td>
<td>PVR &lt; 3 WU</td>
<td></td>
</tr>
<tr>
<td>Combined pre- and post-capillary PH</td>
<td>mPAP &gt; 20 mmHg</td>
<td>2 and 5</td>
</tr>
<tr>
<td>(CpcPH)</td>
<td>PAWP &gt; 15 mmHg</td>
<td></td>
</tr>
<tr>
<td></td>
<td>PVR ≥ 3 WU</td>
<td></td>
</tr>
</tbody>
</table>

mPAP: mean pulmonary arterial pressure; PAWP: pulmonary arterial wedge pressure; PVR: pulmonary vascular resistance; WU: Wood Units. #: group 1: PAH; group 2: PH due to left heart disease; group 3: PH due to lung diseases and/or hypoxia; group 4: PH due to pulmonary artery obstructions; group 5: PH with unclear and/or multifactorial mechanisms.

**Group 1: PAH**

Diagnostic Algorithm

Centers with PAH Expertise

• Whenever possible, all patients should be evaluated promptly at center with PAH expertise

• Preferably prior to initiation of therapy

• Collaborative and closely coordinated care, involving expertise of both local clinicians and those with expertise in PAH care
Evaluate Disease Severity to Inform Treatment Decisions

- Evaluate severity in a systematic and consistent manner
  - WHO FC
  - Exercise capacity
  - Echocardiographic, laboratory and hemodynamic variables

<table>
<thead>
<tr>
<th>Classification</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Class I</td>
<td>Patients with PH but <strong>without resulting limitation</strong> of physical activity. Ordinary physical activity does not cause undue dyspnea or fatigue, chest pain or near syncope.</td>
</tr>
<tr>
<td>Class II</td>
<td>Patients with PH resulting in <strong>slight limitation</strong> of physical activity. They are comfortable at rest. Ordinary physical activity causes undue dyspnea or fatigue, chest pain or near syncope.</td>
</tr>
<tr>
<td>Class III</td>
<td>Patients with PH resulting in <strong>marked limitation</strong> of physical activity. They are comfortable at rest. Less than ordinary activity causes undue dyspnea or fatigue, chest pain or near syncope.</td>
</tr>
<tr>
<td>Class IV</td>
<td>Patients with PH with <strong>inability to carry out</strong> any physical activity without symptoms. These patients manifest signs of right-sided heart failure. Dyspnea and/or fatigue may even be present at rest. Discomfort is increased by any physical activity.</td>
</tr>
</tbody>
</table>
## Currently Approved Medications for PAH

<table>
<thead>
<tr>
<th>Class</th>
<th>Drug</th>
<th>Route of Administration</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prostacyclin derivatives</td>
<td>Epoprostenol*</td>
<td>IV infusion</td>
<td>2 ng/kg/min; increase as tolerated</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Iloprost</td>
<td>Inhaled</td>
<td>2.5 or 5.0 mg; 6-9 inhalations/d</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Treprostinil</td>
<td>Oral</td>
<td>0.25 mg bid or 0.125 mg tid</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Inhaled</td>
<td>Increase 0.125 mg bid every 3-4 d</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Subcutaneous or IV infusion</td>
<td>1.25 ng/kg/min; increase 1.25 ng/kg/min per week based on clinical response</td>
</tr>
<tr>
<td>Endothelin receptor antagonists</td>
<td>Bosentan</td>
<td>Oral</td>
<td>125 mg twice daily</td>
</tr>
<tr>
<td></td>
<td>Ambrisentan</td>
<td>Oral</td>
<td>5 or 10 mg once daily</td>
</tr>
<tr>
<td></td>
<td>Macitentan</td>
<td>Oral</td>
<td>10 mg once daily</td>
</tr>
<tr>
<td>Phosphodiesterase type-5 inhibitors</td>
<td>Sildenafil</td>
<td>Oral</td>
<td>20 mg every 8 h</td>
</tr>
<tr>
<td></td>
<td>Tadalafil</td>
<td>Oral</td>
<td>40 mg once daily</td>
</tr>
<tr>
<td></td>
<td></td>
<td>IV injection</td>
<td></td>
</tr>
<tr>
<td>Soluble guanylate cyclase stimulator</td>
<td>Riociguat</td>
<td>Oral</td>
<td>0.5-1.0 mg every 8 h (increase 0.5 mg every 2 wk as tolerated to maximum dose 2.5 mg)</td>
</tr>
<tr>
<td>Prostacyclin receptor agonists</td>
<td>Selexipag</td>
<td>Oral</td>
<td>200 mg twice daily; increase as tolerated to maximum dose of 1600 mg twice daily</td>
</tr>
</tbody>
</table>
Treatment Goals

• Achieving low-risk status, which is:
  – Good exercise capacity
  – Good quality of life
  – Good RV function
  – Low mortality risk

Goal: WHO-FC II whenever possible, with normal/near-normal 6MWD
Updated CHEST Guidelines

- Two new recommendations on COMBINATION THERAPY
- Two consensus statements on PALLIATIVE CARE

Treatment Naïve Patients: WHO FC II and III

Initial combination therapy with ambrisentan and tadalafil to improve 6MWD

Negative Acute Vasoreactivity Test

- Treatment naïve PAH patients with WHO FC II
  - Is the patient willing or able to tolerate combination therapy?
    - Yes: Combination therapy with ambrisentan and tadalafil
    - No: Combination therapy with ambrisentan and tadalafil, macitentan, ambrisentan, riociguat, sildenafil or tadalafil

- Treatment naïve PAH patients with WHO FC II without evidence of rapid disease progression or poor prognosis
  - Is the patient willing or able to tolerate combination therapy?
    - Yes: Combination therapy with ambrisentan and tadalafil
    - No: Combination therapy with ambrisentan and tadalafil, macitentan, ambrisentan, riociguat, sildenafil or tadalafil
Additional New Recommendations

• For stable or symptomatic patients on background therapy with ambrisentan
  — Add Tadalafil to improve 6MWD

• Incorporate palliative care services in the management of PAH patients

• Patients with PAH should participate in supervised exercise activity as part of the integrated care of their disease

Chronic Thromboembolic Pulmonary Hypertension (CTEPH)
Acute Pulmonary Embolism May Fail to Resolve Leading to CTEPH

**Acute Pulmonary Embolism**
U.S. Incidence: 300,000

**Persistent Perfusion Defects**
Predicted Incidence: 90,000

**Chronic Thromboembolic Disease with Exercise Limitation**
Predicted Incidence: Unknown

**Chronic Thromboembolic Pulmonary Hypertension**
Predicted Incidence: 3,000

**Silent Pulmonary Embolism**
Predicted Incidence: Unknown

Estimates of the annual U.S. incidence of chronic thromboembolic pulmonary hypertension based on the U.S. annual incidence of pulmonary embolism

Clues to CTEPH Present on CT

SCAR: Suspect, Confirm, Assess Risk

Dyspnea after Acute PE

- **Suspect**
  - Echocardiogram
  - VQ scan

- **Confirm**
  - Right heart catheterization
  - Pulmonary angiogram (or CTPA, MRA)

- **Assess Risk**
  - Hemodynamics
  - Comorbidities
  - Surgeon/CTEPH team experience

Unexplained Dyspnea

# CTEPH vs Chronic Thromboembolic Disease

## TABLE 1 Chronic thromboembolic disease (CTED) compared with chronic thromboembolic pulmonary hypertension (CTEPH)

<table>
<thead>
<tr>
<th>Diagnostic criteria</th>
<th>CTEPH</th>
<th>CTED</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptoms</td>
<td>Exercise dyspnoea</td>
<td>Exercise dyspnoea</td>
</tr>
<tr>
<td>PH</td>
<td>Present at rest</td>
<td>Absent at rest</td>
</tr>
<tr>
<td>RHC at exercise</td>
<td>Any mismatched perfusion defect</td>
<td>mPAP/CO slope &gt;3 mmHg L⁻¹·min⁻¹</td>
</tr>
<tr>
<td>V/Q scan</td>
<td>Typical findings of CTEPH</td>
<td>Any mismatched perfusion defect</td>
</tr>
<tr>
<td>Angiography (CTPA or DSA)</td>
<td>Excluding left ventricular myocardial or valvular disease</td>
<td>Typical findings of CTEPH Excluding ventilatory limitation, deconditioning</td>
</tr>
<tr>
<td>CPET</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TTE</td>
<td>At least 3 months</td>
<td>At least 3 months</td>
</tr>
<tr>
<td>Anticoagulation</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

RHC: right heart catheterisation; V/Q: ventilation/perfusion; CTPA: computed tomography pulmonary angiogram; DSA: digital subtraction angiogram; CPET: cardiopulmonary exercise test; TTE: transthoracic echocardiogram; mPAP: mean pulmonary arterial pressure; CO: cardiac output.

VQ Scan Remains Screening Test of Choice
CTEPH Treatment Algorithm

CTEPH diagnosis
Continue lifelong anticoagulation

Treatment assessment by an expert CTEPH team*

Operable
Pulmonary endarterectomy (treatment of choice)

Non-operable
Targeted medical therapy with or without BPA†

Persistent/recurrent symptomatic pulmonary hypertension


- BPA: balloon pulmonary angioplasty
- #: multidisciplinary: pulmonary endarterectomy surgeon, PH expert, BPA interventionist and radiologist
- †: treatment assessment may differ depending on the level of expertise
- +: BPA without medical therapy can be considered in selected cases
PTE Operability Assessment

- Reliable and Precise Imaging
- Surgeon’s Experience
  - #’s, outcomes, distal disease
- Clot Burden
- Center’s Experience
- Patient Factors:
  - Age, comorbidities
- Hemodynamics

---

www.PILOTforPulmonary.org
Favorable Risk-Benefit Assessment for Pulmonary Endarterectomy

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Lower risk with predictable good long-term outcome</th>
<th>Higher risk with less predictable long-term outcome (not contraindications)</th>
</tr>
</thead>
<tbody>
<tr>
<td>History</td>
<td>History of DVT/PE</td>
<td>No history of DVT/PE</td>
</tr>
<tr>
<td>Examination</td>
<td>No signs of right heart failure</td>
<td>Signs of right heart failure</td>
</tr>
<tr>
<td>Comorbidity</td>
<td>None</td>
<td>Significant concomitant lung or left heart disease</td>
</tr>
<tr>
<td>Functional limitation</td>
<td>Functional class II or III</td>
<td>Functional class IV</td>
</tr>
<tr>
<td>Imaging</td>
<td>Clear disease concordant on all images</td>
<td>Inconsistency on imaging modalities</td>
</tr>
<tr>
<td>Type of disease</td>
<td>Bilateral lower lobe disease</td>
<td>No disease appreciable in lower lobes</td>
</tr>
<tr>
<td>Haemodynamics</td>
<td>PVR &lt;$1000 \text{ dyn} \cdot \text{s} \cdot \text{cm}^{-5}$, in proportion to site and number of obstructions on imaging; higher PA pulse pressure</td>
<td>PVR &gt;$1200 \text{ dyn} \cdot \text{s} \cdot \text{cm}^{-5}$, out of proportion to site and number of obstructions on imaging; higher PA diastolic pressure</td>
</tr>
</tbody>
</table>

DVT: deep vein thrombosis; PE: pulmonary embolism; PVR: pulmonary vascular resistance; PA: pulmonary artery.
**CTEPH Survival: Operated vs Non-operated Patients**

**N=679** incident patients with CTEPH included in an international prospective registry over a 24-month period.


**N=112** patients with CTEPH; single center study

Medical Therapy for CTEPH for Patients Deemed Inoperable or with Residual CTEPH

• Targeting the nitric oxide pathway
  – Riociguat: oral, soluble guanylate cyclase stimulator

• Targeting the endothelin pathway
  – Macitentan: oral, endothelin receptor antagonist
CHEST-1: Riociguat Monotherapy for Inoperable or Residual CTEPH

N=261. Double-blind placebo-controlled trial. Patients were not allowed to be on other PAH-specific therapy

WHO Functional Class:
Placebo, 15% moved to lower FC
Riociguat, 33% moved to lower FC

P = 0.003

<table>
<thead>
<tr>
<th>Event</th>
<th>Placebo (n = 88)</th>
<th>Riociguat (n = 173)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any adverse event</td>
<td>86%</td>
<td>92%</td>
</tr>
<tr>
<td>Discontinuation due to study drug</td>
<td>2%</td>
<td>3%</td>
</tr>
<tr>
<td>Headache</td>
<td>14%</td>
<td>25%</td>
</tr>
<tr>
<td>Dizziness</td>
<td>12%</td>
<td>23%</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>8%</td>
<td>18%</td>
</tr>
<tr>
<td>Peripheral edema</td>
<td>20%</td>
<td>16%</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>9%</td>
<td>15%</td>
</tr>
<tr>
<td>Nausea</td>
<td>8%</td>
<td>11%</td>
</tr>
<tr>
<td>Vomiting</td>
<td>3%</td>
<td>10%</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>5%</td>
<td>10%</td>
</tr>
<tr>
<td>Cough</td>
<td>18%</td>
<td>5%</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>14%</td>
<td>5%</td>
</tr>
</tbody>
</table>

*Selected AEs, including those reported in ≥ 10% of patients

MERIT-1: Macitentan for the Treatment of Inoperable CTEPH

- 80 patients, randomized, placebo controlled
- 16-week trial
- Treatment with PDE-5 inhibitors and oral or inhaled prostanoids was permitted for WHO functional class III/IV patients
- Primary endpoint: PVR
- Secondary endpoint:
  - WHO Group, six-minute walk, Borg score, hemodynamics
MERIT-1: Macitentan for the Treatment of Inoperable CTEPH

PVR at Week 16

Change in 6MWD
## Macitentan Safety

<table>
<thead>
<tr>
<th>Event</th>
<th>Macitentan group (n=40)</th>
<th>Placebo group (n=40)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with ≥1 adverse event</td>
<td>30 (75%)</td>
<td>32 (80%)</td>
</tr>
<tr>
<td>Patients with ≥1 serious adverse event</td>
<td>3 (8%)</td>
<td>7 (18%)</td>
</tr>
<tr>
<td>Patients with adverse events leading to discontinuation of study treatment</td>
<td>0</td>
<td>2 (5%)</td>
</tr>
<tr>
<td>Adverse events*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peripheral oedema</td>
<td>9 (23%)</td>
<td>4 (10%)</td>
</tr>
<tr>
<td>Decrease in haemoglobin</td>
<td>6 (15%)</td>
<td>0</td>
</tr>
<tr>
<td>Pain in extremity</td>
<td>3 (8%)</td>
<td>0</td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>3 (8%)</td>
<td>0</td>
</tr>
<tr>
<td>Other adverse events and laboratory findings of interest†</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Haemoptysis</td>
<td>1 (3%)</td>
<td>1 (3%)</td>
</tr>
<tr>
<td>Haemoglobin ≤8 g/dL</td>
<td>0</td>
<td>1 (3%)</td>
</tr>
<tr>
<td>Haemoglobin decrease from baseline ≥2 g/dL</td>
<td>11 (28%)</td>
<td>8 (20%)</td>
</tr>
</tbody>
</table>

PAH and CTEPH Pearls

**PAH**

• Whenever possible, all PAH patients should be evaluated promptly at a center with expertise in the diagnosis of PAH, ideally prior to the initiation of therapy

• Updated CHEST guidelines provide recommendations for combination therapy in treatment naive PAH patients with WHO FC II and III to improve 6MWD

**CTEPH**

• Consider screening for CTEPH in patients with dyspnea after pulmonary embolism and in patients evaluated for PAH
  
  — VQ scan screening test of choice

• Consult with experts at an experienced center for assessment of operability for patients with CTEPH

• For patients with CTEPH deemed inoperable:
  
  — Riociguat: FDA-approved medical therapy
  
  — Macitentan: Data supporting efficacy and safety
  
  — Both riociguat and macitentan carry warnings for embryo-fetal toxicity
Severe Asthma
Asthma Phenotypes and Endotypes

— **Phenotype**: clinical characteristics based upon genetic makeup and environmental exposures

— **Endotype**: specific phenotype with well-characterized pathophysiologic (molecular) mechanism
  
  — **T2 cytokines (IL-4, IL-5, IL-13)**: dominant cytokines in airways of 60–70% of patients with asthma
  
  — **Cell sources of IL-5 and IL-13**: TH2 cells, type 2 innate lymphoid cells (ILC-2), mast cells
  
  — T2 gene expression correlates with worsening asthma control


## Type 2 vs Non-Type 2 Asthma: Basic Distinctions

### Type 2 Asthma
- More severe
- High expression of Th2-cell cytokines in the airways
- Airway and systemic eosinophilia
- Responsive to corticosteroids
- Responsive to inhibitors of type 2 inflammation

### Non-Type 2 Asthma
- Less severe
- Low expression of Th2-cell cytokines in the airways
- Absence of airway and systemic eosinophilia
- Lack of responsiveness to corticosteroids
- Lack of responsiveness to inhibitors of type 2 inflammation
## Severe Asthma Phenotypes and Endotypes

<table>
<thead>
<tr>
<th>Endotype</th>
<th>Phenotype</th>
<th>Clinical/Physiologic Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type 2 with variable eosinophilia</td>
<td>Early-onset, allergic</td>
<td>• History of atopic dermatitis and allergic rhinitis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• May have chronic rhinosinusitis</td>
</tr>
<tr>
<td>Type 2 with marked eosinophilia; leukotrienes important in AERD</td>
<td>Late-onset, less allergic</td>
<td>• Often develops after chronic rhinosinusitis/nasal polyps; may be associated with AERD</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Severe airway obstruction</td>
</tr>
<tr>
<td>Non-Type 2 with minimal or no eosinophilia</td>
<td>Late-onset, obesity-related, nonallergic</td>
<td>• Relatively normal bronchial responsiveness; minimal or no allergic comorbidities</td>
</tr>
<tr>
<td></td>
<td>Late-onset, nonallergic</td>
<td>• Poorly characterized</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• May have significant LRT infection or GERD</td>
</tr>
</tbody>
</table>

*Abbreviations:* AERD = aspirin-exacerbated respiratory disease; LRT = lower respiratory infection; GERD = gastroesophageal reflux disease.

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Target</th>
</tr>
</thead>
<tbody>
<tr>
<td>Omalizumab* (Xolair)</td>
<td>IgE</td>
</tr>
<tr>
<td>Mepolizumab* (Nucala)</td>
<td>IL-5</td>
</tr>
<tr>
<td>Reslizumab* (Cinqair)</td>
<td>IL-5</td>
</tr>
<tr>
<td>Benralizumab* (Fasenra)</td>
<td>IL-5Rα</td>
</tr>
<tr>
<td>Dupilumab* (Dupixent)</td>
<td>IL-4Rα (IL-4, IL-13)</td>
</tr>
<tr>
<td>Tezepelumab‡ (Currently no brand name)</td>
<td>TSLP</td>
</tr>
</tbody>
</table>

*FDA-approved for asthma.
‡Phase 2 clinical trial for treatment of severe asthma is complete; a phase 3 trial is recruiting.
Anti-IgE Therapy: Omalizumab

- Omalizumab decreases FcεRI.
- IgE binds free IgE and inhibits allergen bridging.
- This decreases histamine, prostanoids, and leukotrienes.

**Key Terms:***
- IgE
- Omalizumab
- Antigen/allergen
- FcεRI

**Explanation:**
- B Lymphocyte
- Plasma cell
- Mast cell
- Histamine
- Prostanoids
- Leukotrienes

**Formula:**
- IgE = Y
- Omalizumab = Y
- Antigen/allergen = •
- FcεRI = U
Omalizumab: Pivotal Clinical Trial Findings in Allergic Asthma Uncontrolled with ICS

**Stable Steroid Phase - 16 wks**

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Omalizumab</th>
</tr>
</thead>
<tbody>
<tr>
<td>Busse et al. 2001</td>
<td>0.54</td>
<td>0.66</td>
</tr>
<tr>
<td>Soler et al. 2001</td>
<td>0.28</td>
<td>0.28</td>
</tr>
</tbody>
</table>

**Steroid Reduction Phase - 12 wks**

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Omalizumab</th>
</tr>
</thead>
<tbody>
<tr>
<td>Busse et al. 2001</td>
<td>0.66</td>
<td>0.39</td>
</tr>
<tr>
<td>Soler et al. 2001</td>
<td>0.28</td>
<td>0.36</td>
</tr>
</tbody>
</table>

**Safety**

- In both studies, adverse events occurred at similar rates in both treatment groups
- NOTE: Omalizumab carries a boxed warning for anaphylaxis

[https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/103976s5231lbl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/103976s5231lbl.pdf)
Anti-IL-5 and Anti-IL-5R MABs: Mepolizumab, Reslizumab, Benralizumab

- Reduced eosinophil proliferation
- Reduced eosinophil survival
- Reduced eosinophil maturation
- Eosinophils apoptosis (cells die)

Benralizumab = Y
IL-5Rα = Y
IL-5 = A

www.PILOTforPulmonary.org
Mepolizumab: Effect on Exacerbations in Patients with Severe Eosinophilic Asthma*

Safety findings
- Overall adverse events were similar across treatment groups
- The most common adverse events, occurring at similar rates in all treatment groups, were headache and nasopharyngitis
- In the MENSA study, injection-site reactions were more common in the patients receiving mepolizumab SQ vs IV

*In both studies, patients had to have experienced ≥ 2 exacerbations treated with CS in the past 12 months.

Safety

- Overall adverse events occurred at similar rates in each treatment group; serious adverse events occurred more frequently in the placebo group.
- Two patients receiving reslizumab had anaphylactic reactions; both responded to standard treatment.
- NOTE: Reslizumab carries a boxed warning for anaphylaxis.
Effect of Benralizumab on Exacerbations in Patients with Severe Asthma: SIROCCO Trial

Safety:
- Overall adverse events were similar for all groups
- The most common adverse events, occurring at similar rates in all study groups, were worsening asthma and nasopharyngitis

Dupilumab: MOA in Asthma

Abbreviations: iNOS = inducible nitric oxide synthase; LTs = leukotrienes; ASM = airway smooth muscle cell.

Efficacy of Dupilumab (anti-IL-4/-13R) in Patients with Uncontrolled Asthma: LIBERTY ASTHMA Phase 3 Trials

• Dupilumab also improved FEV1 outcomes and ACQ-5 scores, and reduced hospitalization/ED visit rates.

• Sub-analysis by blood eosinophils and FeNo levels show that dupilumab is most effective in patients with higher values at baseline.

* P<0.001. BL = Baseline.
Efficacy of Dupilumab (anti-IL-4/-13R) in Patients with Uncontrolled Asthma: LIBERTY ASTHMA Phase 3 Trials

VENTURE Phase 3 Trial
210 patients ≥ 12 years with oral corticosteroid-dependent severe asthma

<table>
<thead>
<tr>
<th>Group</th>
<th>Change in OCS Dose from BL (24 weeks)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dupilumab 300 mg 2.00mL</td>
<td>-70 ±5%</td>
</tr>
<tr>
<td>Placebo 2.0 ml</td>
<td>-42 ±5%</td>
</tr>
</tbody>
</table>

48% of patients with corticosteroid-dependent severe asthma no longer needed OCS after 24 weeks of dupilumab vs. 25% of patients in placebo group (P=0.002)

* P<0.001. BL = Baseline.
Asthma Pearls

• Severe or uncontrolled asthma is common and undermanaged
• Evaluating patients to confirm asthma and identify asthma phenotype and endotype can inform treatment decisions that can improve asthma control
• Severe Type 2 asthma includes two main subtypes
  – Early-onset asthma, variable eosinophilia, allergic
  – Later-onset asthma, eosinophilia, non-allergic
• Several MABs that target specific pathways have proven effective and safe in clinical practice
• Improved understanding of asthma pathogenesis and identification of additional relevant biomarkers will be important in developing new antibody therapies
COPD
Pharmacological Management: Key Points

- Pharmacological therapy can reduce COPD symptoms, reduce frequency and severity of exacerbations, and improve health status and exercise tolerance.

- Pharmacological treatment should be individualized and guided by:
  - Symptom severity
  - Risk of exacerbations
  - Side effects
  - Comorbidities
  - Drug availability and cost
  - Patient’s response, preference and ability to use various devices

Inhaler technique needs to be assessed regularly!

2019 GOLD ABCD Assessment Tool

Spirometrically confirmed diagnosis

Assessment of airflow limitation

Assessment of symptoms/risk of exacerbations

Moderate or severe exacerbation history

<table>
<thead>
<tr>
<th>Post-bronchodilator FEV₁/FVC &lt; 0.7</th>
</tr>
</thead>
<tbody>
<tr>
<td>GOLD 1</td>
</tr>
<tr>
<td>GOLD 2</td>
</tr>
<tr>
<td>GOLD 3</td>
</tr>
<tr>
<td>GOLD 4</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>FEV₁ (% predicted)</th>
</tr>
</thead>
<tbody>
<tr>
<td>GOLD 1</td>
</tr>
<tr>
<td>GOLD 2</td>
</tr>
<tr>
<td>GOLD 3</td>
</tr>
<tr>
<td>GOLD 4</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>mMRC 0-1 CAT &lt; 10</th>
</tr>
</thead>
<tbody>
<tr>
<td>mMRC ≥ 2 CAT ≥ 10</td>
</tr>
</tbody>
</table>

Goals for Treatment of Stable COPD

**REDUCE SYMPTOMS**

- Relieve symptoms
- Improve exercise tolerance
- Improve health status

**REDUCE RISK**

- Prevent disease progression
- Prevent and treat exacerbations
- Reduce mortality

---

**Identify & Reduce Risk Factor Exposure**

- Smoking cessation
- Efficient ventilation should be recommended
- Advise patients to avoid continued exposures to the potential irritants

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# Long-Acting Combinations for COPD

<table>
<thead>
<tr>
<th>LAMA/LABA</th>
<th>Dose and Inhalation Device</th>
<th>LABA/ICS</th>
<th>Dose and Inhalation Device</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Once Daily</strong></td>
<td></td>
<td><strong>Once Daily</strong></td>
<td></td>
</tr>
<tr>
<td>Umeclidinium/vilanterol</td>
<td>62.5/25 µg (DPI)</td>
<td>Vilanterol/fluticasone furoate</td>
<td>25 µg/100 µg (DPI) daily</td>
</tr>
<tr>
<td>Tiotropium/olodaterol</td>
<td>5/5 µg (SMI)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Twice Daily</strong></td>
<td></td>
<td><strong>Twice Daily</strong></td>
<td></td>
</tr>
<tr>
<td>Glycopyrrolate/formoterol</td>
<td>18/9.6 µg (MDI)</td>
<td>Formoterol/budesonide</td>
<td>4.5 µg/160 µg (MDI)</td>
</tr>
<tr>
<td>Indacaterol/glycopyrrolate</td>
<td>27.5/15.6 µg (DPI)</td>
<td>Formoterol/mometasone</td>
<td>5 µg/100 µg or 5 µg/200 µg (MDI)</td>
</tr>
<tr>
<td><strong>ICS/LAMA/LABA</strong></td>
<td><strong>Dose and Inhalation Device</strong></td>
<td><strong>Salmeterol/fluticasone</strong></td>
<td>50 µg/250 µg (DPI)</td>
</tr>
<tr>
<td><strong>Once Daily</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fluticasone/umeclidinium/vilanterol</td>
<td>100 µg/62.5/25 µg (DPI)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Inhaled Therapies

• When a treatment is given by the inhaled route, the importance of education and training in inhaler device technique cannot be over-emphasized.

• The choice of inhaler device has to be individually tailored and will depend on access, cost, and most importantly, patient’s ability and preference.

• It is essential to provide instructions and demonstrate the proper inhalation technique when prescribing a device to ensure that inhaler technique is adequate and re-check at each visit that patients continue to use their inhaler correctly.

• Inhaler technique (and adherence to therapy) should be assessed before concluding that the current therapy is insufficient.
# Initial Pharmacological Treatment

<table>
<thead>
<tr>
<th>Group C</th>
<th>LAMA</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ 2 moderate exacerbations or ≥ 1 leading to hospitalization</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Group D</th>
<th>LAMA or LAMA + LABA* or ICS + LABA**</th>
</tr>
</thead>
<tbody>
<tr>
<td>*Consider if highly symptomatic (e.g. CAT &gt; 20)</td>
<td></td>
</tr>
<tr>
<td>**Consider if eos ≥ 300</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Group A</th>
<th>A Bronchodilator</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 or 1 moderate exacerbations (not leading to hospital admission)</td>
<td></td>
</tr>
</tbody>
</table>

| mCRC 0-1 CAT < 10 |

<table>
<thead>
<tr>
<th>Group B</th>
<th>A Long-Acting Bronchodilator (LABA or LAMA)</th>
</tr>
</thead>
<tbody>
<tr>
<td>mCRC ≥ 2 CAT ≥ 10</td>
<td></td>
</tr>
</tbody>
</table>

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COPD Management Cycle

REVIEW
- Symptoms
  - Dyspnea
  - Exacerbations

ADJUST
- Escalate
- Switch inhaler device or molecules
- De-escalate

ASSESS
- Inhaler technique and adherence
- Non-pharmacological approaches (including pulmonary rehabilitation and self-management education)

If Response to Treatment Is Not Adequate

**Dyspnea**

- LABA or LAMA
  - Consider switching inhaler device or molecules
  - Investigate (and treat) other causes of dyspnea
- LABA + LAMA
- LABA + LAMA + ICS

**Exacerbations**

- LABA or LAMA
- LABA + LAMA
- LABA + LAMA + ICS
- LABA + LAMA + ICS

**EOS**

- Eos = blood eosinophil count (cells/µl)
  - Consider if eos ≥ 300 or eos ≥ 100 AND ≥ 2 moderate exacerbations / 1 hospitalization
  - ** Consider de-escalation of ICS or switch if pneumonia, inappropriate original indication or lack of response to ICS

Non-Pharmacological Management: Key Points

- Patient education and self-management
- Influenza and pneumococcal vaccines decrease the incidence of lower respiratory tract infections
- Pulmonary rehabilitation improves symptoms, quality of life and physical/emotional participation in everyday activities
- In patients with severe resting chronic hypoxemia, long-term oxygen therapy improves survival
- Palliative approaches are effective in controlling symptoms in advanced COPD

COPD Pearls

• Pharmacological treatment for COPD should be individualized and guided by:
  – Symptom severity
  – Risk of exacerbations
  – Side effects
  – Comorbidities
  – Drug availability and cost
  – Patient’s response, preference and ability to use various devices

• Following implementation of therapy, review, assess for attainment of treatment goals and adjust treatment as indicated

• For inhaled therapies, demonstrate proper inhalation technique, confirm and re-check at each visit

• Don’t forget non-pharmacological therapies!