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Diagnosis of Idiopathic Pulmonary Fibrosis; An Official ATS/ERS/JRS/ALAT Clinical Practice Guideline

Am J Respir Crit Care Med 2018;198(5):e44–e68.
https://doi.org/10.1164/rccm.201807-1255ST

Comments: This 2018 guideline updates with ATS/ERS/JRS/ALAT recommendation for the diagnosis of idiopathic pulmonary fibrosis (IPF) from 2011. The guideline panel updated the diagnostic criteria for IPF of high-resolution computed tomography (HRCT) scanning pattern were refined to patterns of usual interstitial pneumonia (UIP), probable UIP, indeterminate for UIP, and alternate diagnosis. Histopathologic patterns and feature were also refined same patterns. For patients with newly detected interstitial lung disease (ILD) who have a HRCT scan pattern of probable UIP, indeterminate for UIP, or an alternative diagnosis, conditional recommendations were made for performing BAL and surgical lung biopsy. Because of lack of evidence, no recommendation was made for or against performing transbronchial lung biopsy or lung cryobiopsy. In contrast, for patients with newly detected ILD who have a HRCT scan pattern of UIP, strong recommendations were made against performing surgical lung biopsy or others. Additional recommendations included a conditional recommendation for multidisciplinary discussion and a strong recommendation against measurement of serum biomarkers including matrix metalloproteinase (MMP)-7, surfactant protein D (SPD), chemokine ligand (CCL)-18, and Krebs von den Lungen (KL)-6 for the sole purpose of distinguishing IPF from other ILDs.

Recommend further readings:
https://doi.org/10.1183/13993003.01485-2018

**Nintedanib plus Sildenafil in Patients with Idiopathic Pulmonary Fibrosis**

Kolb M, et al

https://doi.org/10.1056/NEJMoa1811737

**Comments:** This research conducted randomized, double-blind, parallel-group trial, in a 1:1 ratio, patients with IPF and a DL_{CO} of 35% or less of the predicted value to receive nintedanib-plus-sildenafil group (nintedanib 150 mg twice daily plus sildenafil 20 mg three times daily, n=137) or nintedanib group (nintedanib 150 mg twice daily plus placebo three times daily, n=136) for 24 weeks. A total of 274 patients were randomized (1 was not treated). There was no significant difference in the adjusted mean change from baseline in the SGRQ total score at week 12 comparing two groups. In addition, sildenafil treatment had no benefit with regard to dyspnea and no new safety signals were observed. Combination therapy with nintedanib plus sildenafil did not provide a significant benefit than nintedanib alone in patients with IPF and severe impairment in gas exchange. This study had limitations include the potential underpowering of the trial and its relatively short duration (INSTAGE trial).

**Most cited articles:**
Nintedanib with Add-on Pirfenidone in Idiopathic Pulmonary Fibrosis: Results of the INJOURNEY Trial

Vancheri C, et al


https://doi.org/10.1164/rccm.201706-1301OC

Comments: Patients with IPF and FVC greater than or equal to 50% predicted at screening who completed a 4- to 5-week run-in with nintedanib 150 mg twice daily without dose reduction or treatment interruption were randomized to receive nintedanib 150 mg twice daily with add-on pirfenidone or nintedanib 150 mg twice daily alone in an open-label manner for 12 weeks. On-treatment gastrointestinal adverse events were reported in 37 of 53 patients (69.8%) treated with nintedanib with add-on pirfenidone and 27 of 51 patients (52.9%) treated with nintedanib alone. Predose plasma trough concentrations of nintedanib were similar when it was administered alone or with add-on pirfenidone. Mean (SE) changes from baseline in FVC at Week 12 were −13.3 (17.4) ml and −40.9 (31.4) ml in patients treated with nintedanib with add-on pirfenidone (n = 48) and nintedanib alone (n = 44), respectively. But these results should be interpreted with caution, because this trial was not powered for this endpoint and was too short for conclusions to be drawn about the efficacy of combination therapy. Treatment with nintedanib and add-on pirfenidone for 12 weeks had a manageable safety and tolerability profile in patients with IPF, in line with the adverse event profiles of each drug. Further large controlled studies are needed to confirm the benefit/risk ratio of combination antifibrotic therapy in patients with IPF (INJOURNEY trial).
Safety of nintedanib added to pirfenidone treatment for idiopathic pulmonary fibrosis


Eur Respir J 2018;52:1800230

https://doi.org/10.1183/13993003.00230-2018

Comments: This research assessed safety and tolerability of combined treatment with pirfenidone (1602~2403 mg per day) and nintedanib (200~300 mg per day) in patients with IPF. This 24-week, single-arm, open-label, phase IV study enrolled patients with IPF with % pred forced vital capacity (FVC) $\geq$ 50% and % pred diffusing capacity of the lung for carbon monoxide (DLCo) $\geq$ 30%. Before initiating nintedanib, patients had received pirfenidone for $\geq$ 16 weeks and tolerated a stable dose of $\geq$ 1602 mg per day for $\geq$ 28 days. 89 patients were enrolled; 73 completed 24 weeks of treatment (69 meeting the primary end-point) and 16 discontinued treatment prematurely (13 due to treatment-emergent adverse events (TEAEs)). 74 patients had 418 treatment-related TEAEs, of which diarrhea, nausea and vomiting were the most common. Although the frequency of some TEAEs was higher in this 24-week study than in studies of each therapy alone, discontinuation rates (18% overall and 15% due to TEAEs) were numerically lower than those over 12 weeks in the INJOURNEY trial and over 52 weeks in the INPULSIS trials, and numerically similar to those over 52 weeks or more in the ASCEND and CAPACITY trials. Combined pirfenidone and nintedanib was tolerated by the majority of patients with IPF, encouraging further study.
Long-term safety and tolerability of nintedanib in patients with idiopathic pulmonary fibrosis: results from the open-label extension study, INPULSIS-ON

Crestani B, et al.

Lancet Respir Med 2019;7:60–68

https://www.thelancet.com/journals/lanres/article/PIIS2213-2600(18)30339-4/fulltext

Comments: Patients who completed the 52-week treatment period of INPULSIS, and the follow-up visit 4 weeks later, were eligible for INPULSIS-ON. They received nintedanib 100 or 150 mg twice daily. Of 807 patients who completed the INPULSIS trials, 734 (91%) were treated in INPULSIS-ON. 430 (59%) patients had received nintedanib in INPULSIS and continued nintedanib in INPULSIS-ON, and 304 (41%) had received placebo in INPULSIS and initiated nintedanib in INPULSIS-ON. Median exposure time for patients treated with nintedanib in both the INPULSIS and INPULSIS-ON trials was 44.7 months (range 11.9–68.3). The safety profile of nintedanib in INPULSIS-ON was consistent with that observed in INPULSIS. Diarrhea was the most frequent adverse event in INPULSIS-ON (60.1 events per 100 patient exposure-years in patients who continued nintedanib). The adverse event that most frequently led to permanent discontinuation of nintedanib. The event rate of bleeding was 8.4 events per 100 patient exposure-years in patients who continued nintedanib and major adverse cardiovascular events was 3.6 events per 100 patient exposure-years in patients who continued nintedanib. Continued treatment with nintedanib, for up to 68 months, had a manageable safety and tolerability profile, with no new safety signals identified. Patients with IPF could use nintedanib over the long-term to slow disease progression.
Long-term safety of pirfenidone: results of the prospective, observational PASSPORT study

Cottin V, et al.

ERJ Open Res 2018;4: 00084-2018

https://doi.org/10.1183/23120541.00084-2018

Comments: PASSPORT study was a multicentre, prospective, post-authorisation study of patients who were newly prescribed pirfenidone and followed for 2 years after initiating treatment. Patients (n=1009, 99.7% with idiopathic pulmonary fibrosis) had a median pirfenidone exposure of 442.0 days. Overall, 741 (73.4%) patients experienced adverse drug reactions (ADRs), most commonly nausea (20.6%) and fatigue (18.5%). ADRs led to treatment discontinuation in 290 (28.7%) patients after a median of 99.5 days. Overall, 55 (5.5%) patients experienced serious ADRs (SADRs), with a fatal outcome in 6 patients. ADRs of special interest (ADRSI) were reported in 693 patients, most commonly gastrointestinal symptoms (38.3%) and photosensitivity reactions/skin rashes (29.0%). Older age and female sex were associated with early treatment discontinuation due to an ADR. These findings were consistent with the known safety profile of pirfenidone, based on RCT data, with no new safety signals observed. ADRs were self-reported and only collected at 3-monthly visits, potentially leading to patient recall bias. Data regarding efficacy (e.g. lung function or exercise capacity) were not collected in PASSPORT study.

In this month’s issue of Respirology:

Effect of Recombinant Human Pentraxin 2 vs Placebo on Change in Forced Vital Capacity in Patients With Idiopathic Pulmonary Fibrosis; A Randomized Clinical Trial


JAMA 2018;319(22):2299-2307

https://doi.org/10.1001/jama.2018.6129

Comments: Phase 2, randomized, double-blind, placebo-controlled trial conducted at 18 sites in patients with IPF (N = 117; aged 40-80 years; FVC 5 0% ~ 90% predicted; FEV1/FVC >0.70; DLCO 25% ~ 90% predicted; and distance of ≥ 150 m on the 6-minute walk test (6MWT). Patients were randomized and treatment with recombinant human pentraxin 2 (10 mg/kg intravenous every 4 weeks, n = 77) or placebo (n = 39) for 24 weeks. Of 117 randomized patients, 111 (95.7%) completed the study. Recombinant human pentraxin 2 resulted in a change in FVC percentage of predicted value of −2.5% compared with −4.8% with placebo, a difference that was statistically significant. No significant treatment differences were observed in total lung volume, quantitative parenchymal features on HRCT, or measurement of DLCO. The change in 6MWD was −0.5 m for patients treated with recombinant human pentraxin 2 vs −31.8 m for those in the placebo group. The most common adverse events in the recombinant human pentraxin 2 vs placebo group were cough (18% vs 5%), fatigue (17% vs 10%), and nasopharyngitis (16% vs 23%). Recombinant human pentraxin 2 infusions were well tolerated. In this preliminary study, recombinant human pentraxin 2 resulted in a slower decline in lung function over 28 weeks for patients with IPF, but more definitive research is required.

Recommended further reading: Maher TM, et al. Safety, tolerability, pharmacokinetics, and

**Diagnosis of Chronic Identification of Diagnostic Criteria for Chronic Hypersensitivity Pneumonitis: An International Modified Delphi Survey**

Morisset J, et al.

Am J Respir Crit Care Med 2018;197(8):1036–1044.

http://dx.doi.org/10.1164/rccm.201710-1986OC

**Comments:** Current diagnosis of chronic hypersensitivity pneumonitis (cHP) involves considering a combination of clinical, radiological, and pathological information in multidisciplinary team discussions. The researchers aimed to identify diagnostic criteria for cHP that reach consensus among international experts. A 3-round modified Delphi survey was conducted. Forty-five experts in ILD from 14 countries participated in the online survey. Diagnostic items included in round 1 were generated using expert interviews and literature review. During rounds 1 and 2, experts rated the importance of each diagnostic item on a 5-point Likert scale. In the third round, experts graded the items that met consensus as important and provided their level of diagnostic confidence for a series of clinical scenarios. Consensus was achieved on 18 of the 40 diagnostic items. Experts gave the highest level of importance to the identification of a causative antigen, time relation between exposure and disease, mosaic attenuation on chest imaging, and poorly formed non-necrotizing granulomas on pathology. In clinical scenarios, the diagnostic confidence of experts in cHP was heightened by the presence of these diagnostic items. Using a series of clinical scenarios, which combinations of diagnostic items experts considered
necessary to make a confident diagnosis of cHP. Two different scenario types were felt to represent a confident diagnosis of cHP: 1) combination of identified antigen on history, HRCT features suggestive of cHP, and BAL lymphocytosis greater than 40%; and 2) any scenario that included an identified exposure and lung biopsy with features suggestive of cHP. None of the scenarios that lacked exposure identification were believed to achieve a confident diagnosis even after the inclusion of features suggestive of cHP on lung biopsy. This consensus-based approach for the diagnosis of cHP represents a first step towards the development of international guidelines for the diagnosis of cHP.

**Recommended further reading:** Salisbury ML, et al. Development and validation of a radiological diagnosis model for hypersensitivity pneumonitis. Eur Respir J 2018;52:1800443

[https://doi.org/10.1183/13993003.00443-2018](https://doi.org/10.1183/13993003.00443-2018)

**Deep learning for classifying fibrotic lung disease on high-resolution computed tomography: a case-cohort study**

Walsh SLF, et al.

Lancet Respir Med 2018;6:837–45

[http://dx.doi.org/10.1016/S2213-2600(18)30286-8](http://dx.doi.org/10.1016/S2213-2600(18)30286-8)

**Comments:** HRCT scan plays a central part in the diagnosis of fibrotic lung disease (FLD). The researchers investigated the use of a deep learning algorithm for provision of automated classification of FLD on HRCT according to criteria specified in two international diagnostic guideline statements: the 2011 ATS/ERS/JRS/ALAT guidelines and the Fleischner Society diagnostic criteria for IPF. For algorithm development and testing, a database of 1157 anonymised HRCT scans showing evidence of diffuse FLD was generated from two institutions. The
authors separated the scans into three non-overlapping cohorts (training set, n=929; validation set, n=89; and test set A, n=139) and classified them using 2011 diagnostic guidelines. The final training dataset consisted of 420096 unique montages for algorithm training. This article evaluated algorithm performance, reported as accuracy, prognostic accuracy, and weighted κ coefficient (κw) of interobserver agreement, on test set A and a cohort of 150 HRCT scans (test set B) with FLD compared with the majority vote of 91 specialist thoracic radiologists. The accuracy of the algorithm on test set A was 76·4%, with 92·7% of diagnoses within one category. The algorithm took 2·31 s to evaluate 150 four slice montages (each montage representing a single case from test set B). The median accuracy of the thoracic radiologists on test set B was 70·7%, and the accuracy of the algorithm was 73·3% (93·3% were within one category), outperforming 60 (66%) of 91 thoracic radiologists. Median interobserver agreement between each of the thoracic radiologists and the radiologist's majority opinion was good (κw=0·67). Interobserver agreement between the algorithm and the radiologist's majority opinion was good (κw=0·69), outperforming 56 (62%) of 91 thoracic radiologists. The algorithm provided equally prognostic discrimination between usual interstitial pneumonia (UIP) and non-UIP diagnoses compared with the majority opinion of the thoracic radiologists. For Fleischner Society HRCT criteria for UIP, median interobserver agreement between the radiologists was moderate (κw=0·56), but was good between the algorithm and the radiologists (κw=0·64). HRCT evaluation by a deep learning algorithm might provide low-cost, reproducible, near-instantaneous classification of FLD with human-level accuracy. These methods could be of benefit to centers at which thoracic imaging expertise is scarce, as well as for stratification of patients in clinical trials.
Diagnosis and management of pulmonary toxicity associated with cancer immunotherapy

Rashdan S, Minna JD, Gerber DE

Lancet Respir Med 2018;6:472-78

http://dx.doi.org/10.1016/S2213-2600(18)30172-3

Comments: Pulmonary toxicity of cancer immunotherapies has emerged as an important clinical event that requires prompt identification and management. Although often referred to as pneumonitis, pulmonary toxicity associated with immunotherapy covers a broad and overlapping spectrum of pulmonary manifestations, and, once suspected, the range of differential diagnoses of infectious and neoplastic processes might make the diagnostic process challenging for physicians. This article gives an overview of the diagnosis and management of pulmonary toxicity arising from cancer immunotherapy, including widely used treatments, such as immune checkpoint inhibitors, and emerging therapies, such as chimeric antigen receptor T cells. Immune-related adverse events might occur in more than 25% of patients with cancer treated with immunotherapy; these toxicities occur when host immune cells attack normal tissues. Immune-related adverse events are unpredictable, potentially severe, and can affect almost every organ system. The establishment of a diagnosis of immune-related pulmonary toxicity is challenging - the approach might require radiographic and bronchoscopic evaluation, and therefore might benefit from multidisciplinary collaboration between pulmonary medicine physicians and medical oncologists. The mainstay of management of pulmonary toxicity and other immune-related adverse events is to withhold immunotherapy and administer glucocorticoids. Generally, patients with symptomatic pneumonitis are promptly started on corticosteroids (commonly the equivalent of prednisone 1 mg/kg daily).29,40 Tapering (often by 10 mg/week) begins after im-
Improvement to baseline of symptoms (or mild symptoms only) has occurred. With this approach, steroid courses might last months rather than weeks. In cases refractory to steroids, additional immunosuppressive agents might be considered, including infliximab, cyclophosphamide, or mycophenolate mofetil.