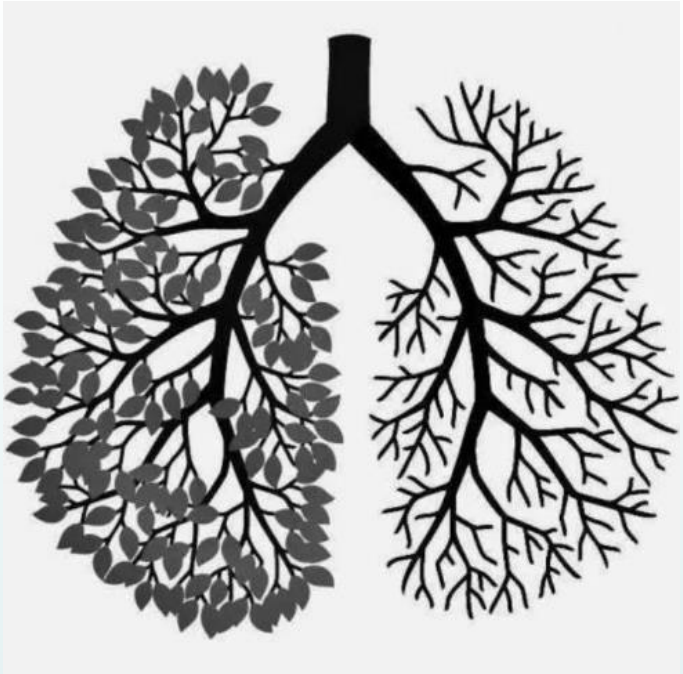

Latest advances in asthma, COPD and ILD

6th Dec 2023

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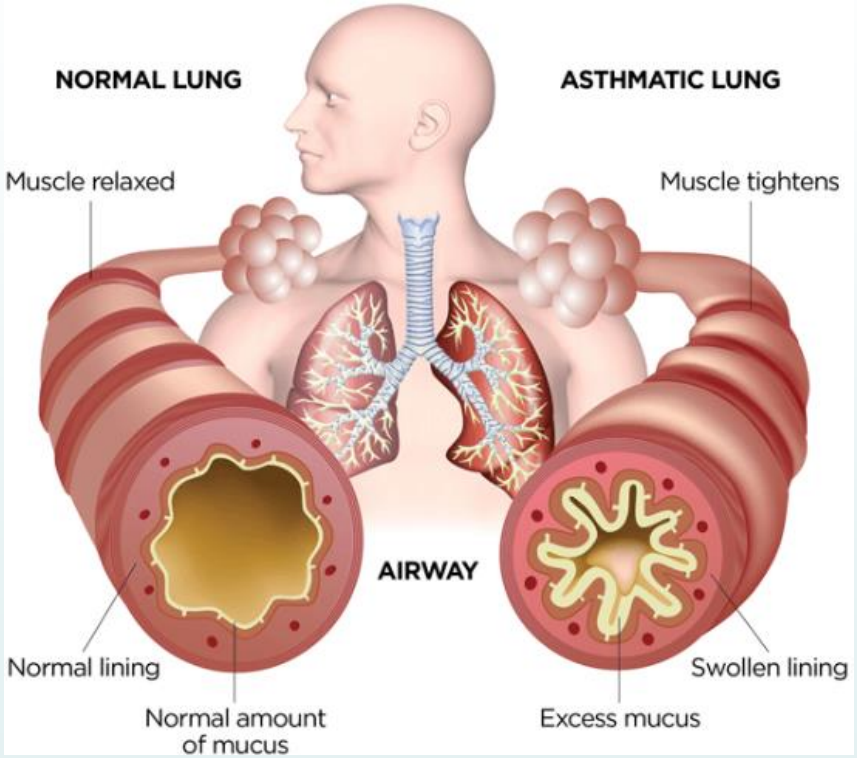
MBBS (Newcastle UK) MRCP (UK) CCT (General Internal and Respiratory Med)

Outline

- Asthma
  - Latest from GINA
  - Biologic therapy
- Chronic obstructive Pulmonary Disease
  - Latest from GOLD (2023 & 2024)
  - Surgical perspectives
- Interstitial lung diseases
  - Antifibrotics
  - CTD-ILDs

Asthma

Asthma

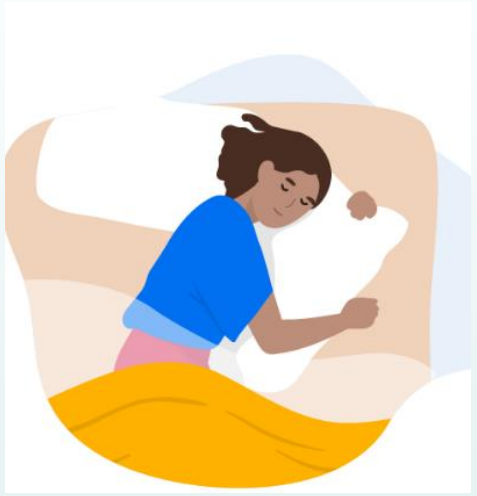


VARIABLE symptoms over time and space

REVERSIBLE airways obstruction

What is good asthma control?

Different patients will have different perspectives as asthma is a HETEROGENEOUS disease



Goals of asthma treatment

- Few asthma symptoms
- No sleep disturbance
- No exercise limitation

} Symptom control (e.g. ACT, ACQ)

- Maintain normal lung function
- Prevent flare-ups (exacerbations)
- Prevent asthma deaths
- Minimize medication side-effects (including OCS)

} Risk reduction

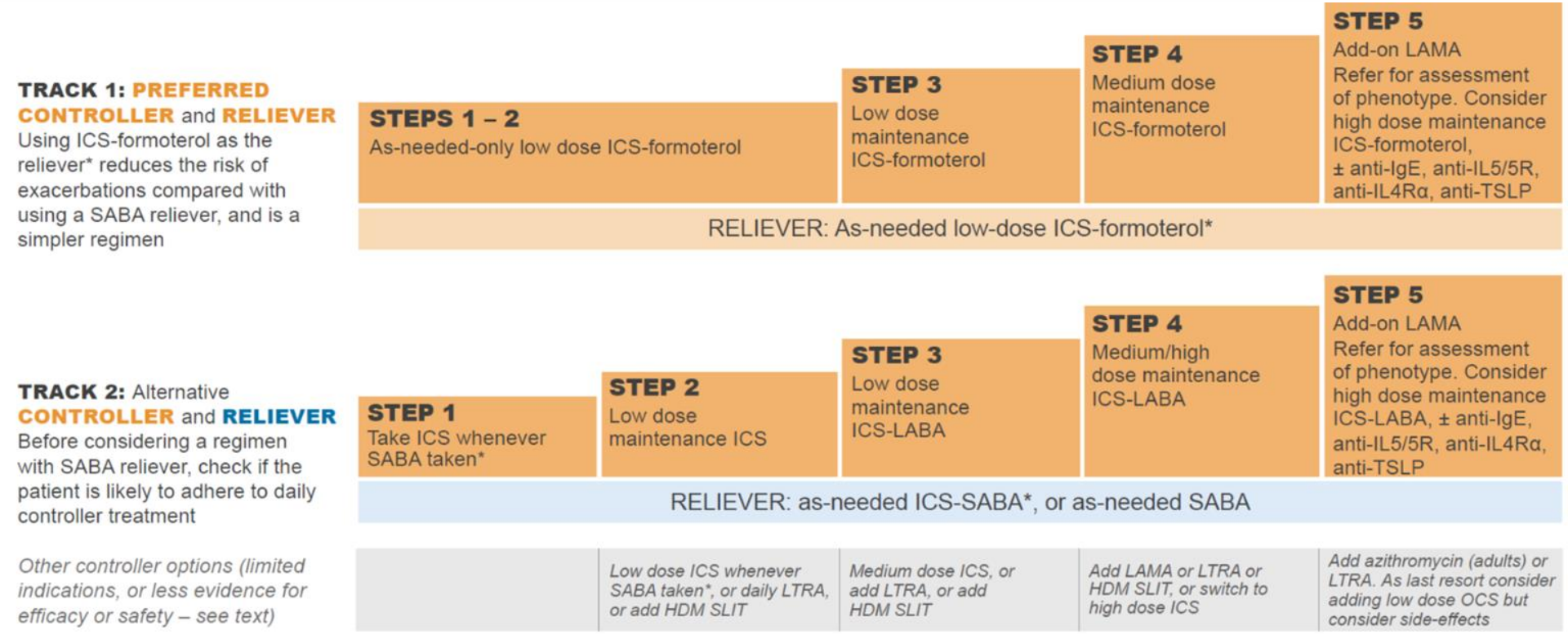
- The patient's goals may be different
- Symptom control and risk may be discordant
  - Patients with few symptoms can still have severe exacerbations

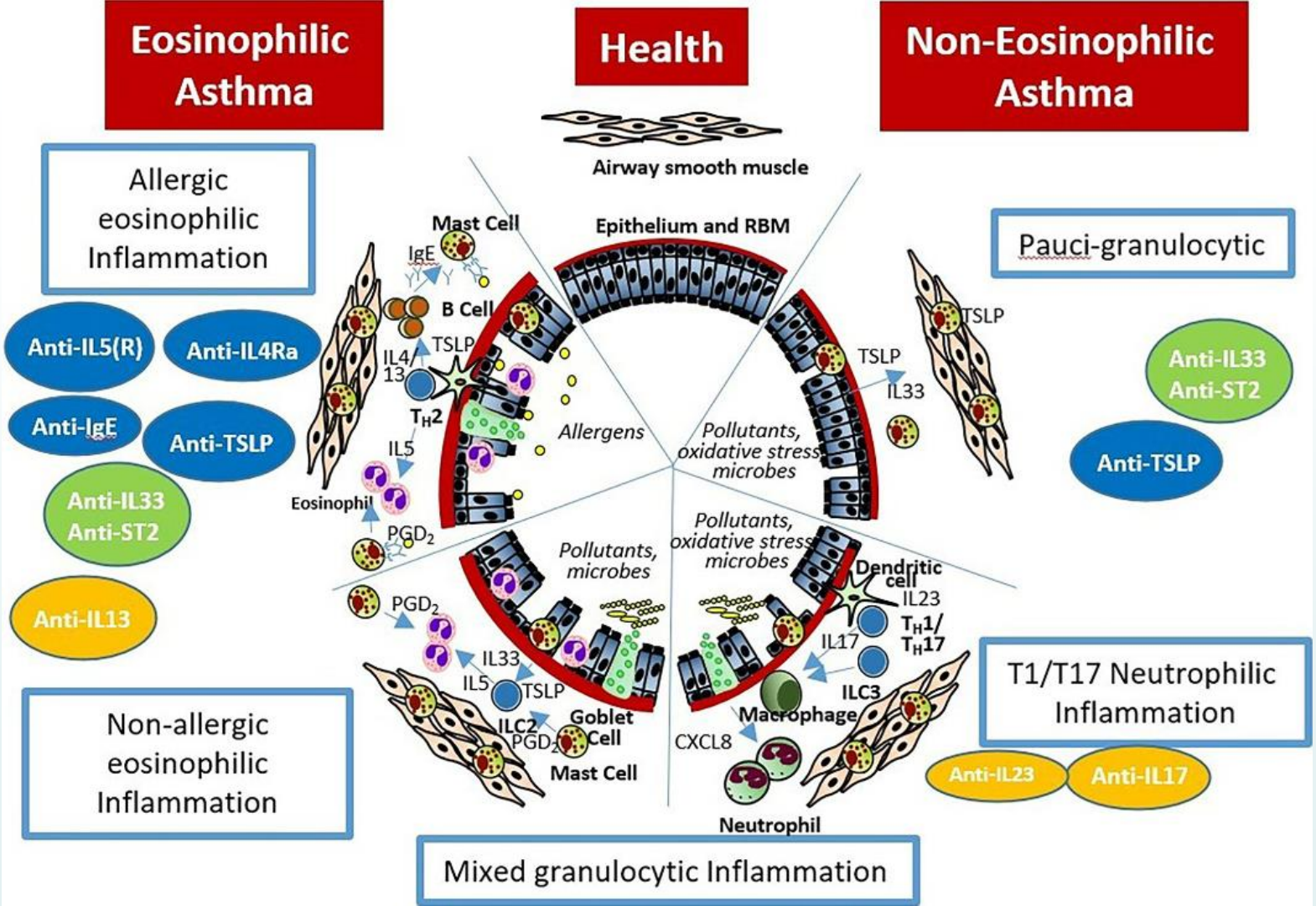
ACQ: Asthma Control Questionnaire; ACT: Asthma Control Test; OCS: oral corticosteroids

GINA 2023 - What's new?

- Adults, adolescents and children aged between 6 and 11 years with asthma should receive inhaled corticosteroid (ICS)-containing medication, and should **NOT** be treated with SABA alone.

- The 2023 GINA strategy divides treatment for adults and adolescents into two 'Tracks' for simplicity
  a. Track 1: the reliever is as-needed combination low-dose **ICS-formoterol**; *this is the preferred treatment option*
  b. Track 2: SABA as the reliever along with a separate preventer inhaler, and is an alternative treatment approach.


TRACK 1: PREFERRED CONTROLLER and RELIEVER
Using ICS-formoterol as the reliever* reduces the risk of exacerbations compared with using a SABA reliever, and is a simpler regimen
STEPS 1 – 2
As-needed-only low dose ICS-formoterol
STEP 3
Low dose maintenance ICS-formoterol
STEP 4
Medium dose maintenance ICS-formoterol
STEP 5
Add-on LAMA
Refer for assessment of phenotype. Consider high dose maintenance ICS-formoterol, ± anti-IgE, anti-IL5/5R, anti-IL4Rα, anti-TSLP
RELIEVER: As-needed low-dose ICS-formoterol*
TRACK 2: Alternative CONTROLLER and RELIEVER
Before considering a regimen with SABA reliever, check if the patient is likely to adhere to daily controller treatment
STEP 1
Take ICS whenever SABA taken*
STEP 2
Low dose maintenance ICS
STEP 3
Low dose maintenance ICS-LABA
STEP 4
Medium/high dose maintenance ICS-LABA
STEP 5
Add-on LAMA
Refer for assessment of phenotype. Consider high dose maintenance ICS-LABA, ± anti-IgE, anti-IL5/5R, anti-IL4Rα, anti-TSLP
RELIEVER: as-needed ICS-SABA*, or as-needed SABA
Other controller options (limited indications, or less evidence for efficacy or safety – see text)
Low dose ICS whenever SABA taken*, or daily LTRA, or add HDM SLIT
Medium dose ICS, or add LTRA, or add HDM SLIT
Add LAMA or LTRA or HDM SLIT, or switch to high dose ICS
Add azithromycin (adults) or LTRA. As last resort consider adding low dose OCS but consider side-effects


Eosinophilic Asthma
Health
Non-Eosinophilic Asthma
Airway smooth muscle
Allergic eosinophilic Inflammation
Mast Cell
IgE
B Cell
TSLP
IL4/13
T_H2
IL5
Eosinophil
PGD_2
Epithelium and RBM
Allergens
Pollutants, oxidative stress microbes
TSLP
IL33
Pauci-granulocytic
Anti-IL5(R)
Anti-IL4Ra
Anti-IgE
Anti-TSLP
Anti-IL33 Anti-ST2
Anti-IL13
Anti-IL33 Anti-ST2
Anti-TSLP
Pollutants, microbes
Pollutants, oxidative stress microbes
Dendritic cell
IL23
T_H1/T_H17
IL17
ILC3
Macrophage
CXCL8
Neutrophil
IL33
IL5
TSLP
ILC2
Goblet Cell
PGD_2
Mast Cell
Non-allergic eosinophilic Inflammation
T1/T17 Neutrophilic Inflammation
Anti-IL23
Anti-IL17
Mixed granulocytic Inflammation

Biologic therapy in Asthma

Biologic (Target)	Omalizumab (IgE)	Mepolizumab (IL5)	Reslizumab (IL5)	Benralizumab (IL-5Rα)	Dupilumab (IL-4Rα)	Tezepelumab (TLSP)
Administration	s/c 2-4 weekly	s/c 4 weekly	IV 4 weekly	s/c 4 weekly, then 8 weekly	s/c 2 weekly	s/c 4 weekly
GINA eligibility criteria	Severe exacerbations within last year, sensitization to inhaled allergens, **total serum IgE** and weight within local dosing range	Severe exacerbations within last year, **blood eosinophil** ≥150 cells/μL or ≥300 cells/μL (locally specified)	Severe exacerbations within last year, **blood eosinophil** ≥150 cells/μL or ≥300 cells/μL (locally specified	Severe exacerbations within last year, **blood eosinophil** ≥150 cells/μL or ≥300 cells/μL (locally specified)	Severe exacerbations within last year, **blood eosinophil** ≥150 cells/μL and ≤1500 cells/μL, or **FeNO** ≥25 ppb, or maintenance OCS	Severe exacerbations within last year
Age	6 and over	12 and over	18 and over	18 and over	12 and over	12 and over
Additional benefits	Nasal polyposis, chronic idiopathic urticaria	Nasal polyposis, EGPA, hypereosinophilic		EGPA, hypereosinophilic syndrome	Moderate–severe atopic dermatitis, CRS and nasal	With or without elevated T2 markers

COPD

COPD - Common, Preventable, Treatable

- Over 3 million COPD deaths in 2022
- *"**heterogeneous lung condition characterized by chronic respiratory symptoms (dyspnea, cough, expectoration and/or exacerbations) due to abnormalities of the airways (bronchitis, bronchiolitis) and/or alveoli (emphysema) that cause persistent, often progressive, airflow obstruction**."*
- Important to have accurate early diagnosis to impact positively on individual's health
    - BUT extensive underdiagnosis and misdiagnosis
    - Precursor conditions: pre-COPD and PRISM (Preserved Ratio Impaired Spirometry) open windows for earlier interventions

NOT just about cigarettes

Non smoking risk factors account for over 50% of the global burden of COPD .

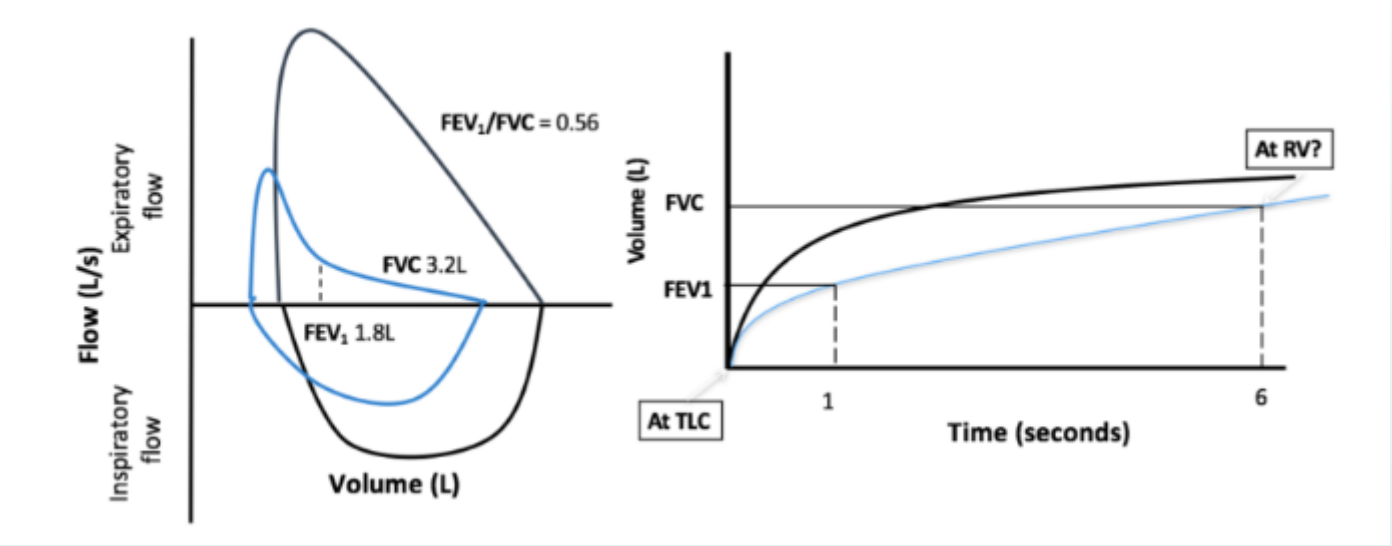
Wood, animal dung, crop residues, and coal (*i.e. biomass*), typically burned in poorly functioning stoves, may lead to very high levels of household air pollution , which is associated with increased COPD risk

Occupational exposures, including organic and inorganic dusts, chemical agents, and fumes, are an under-appreciated environmental risk factor for COPD

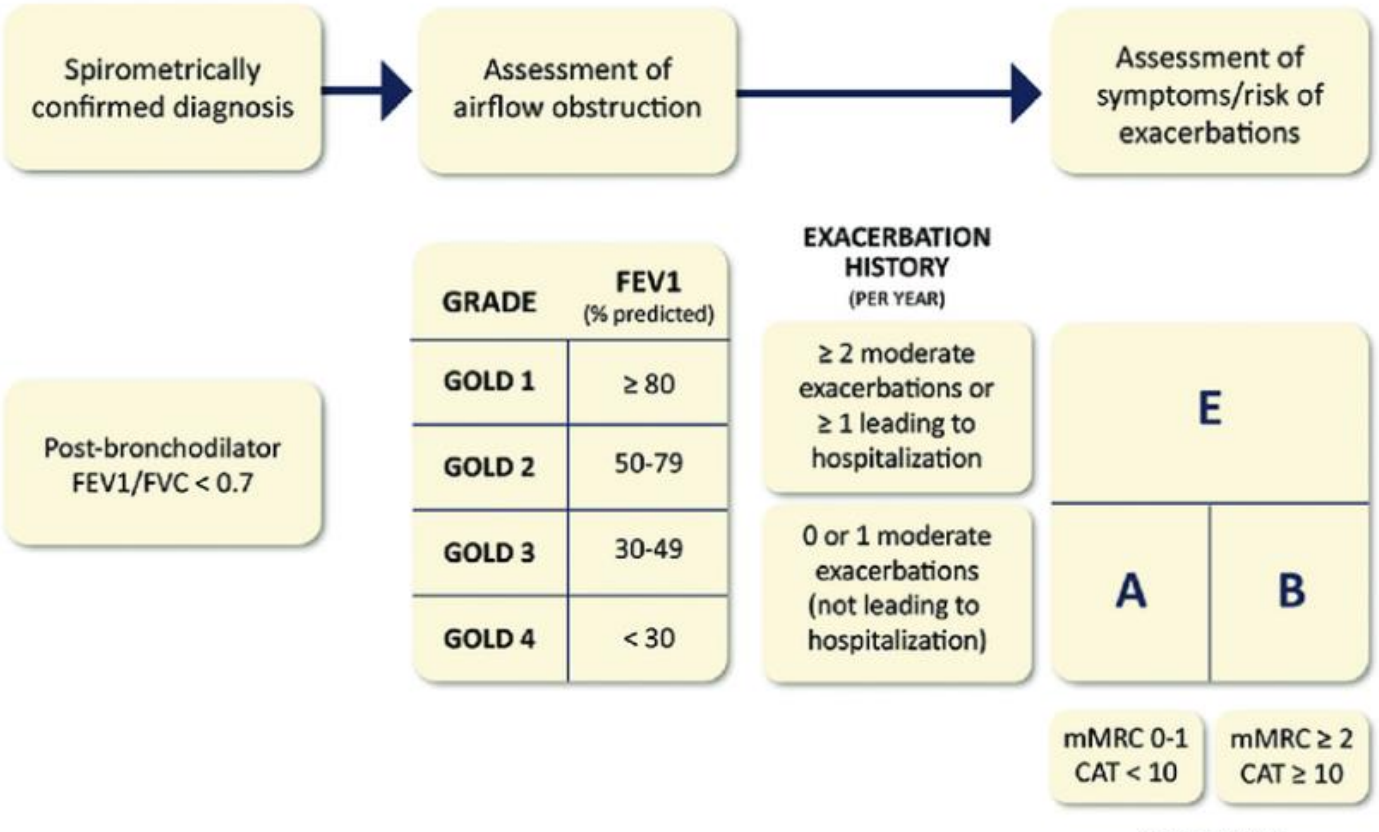
COPD - Diagnosis

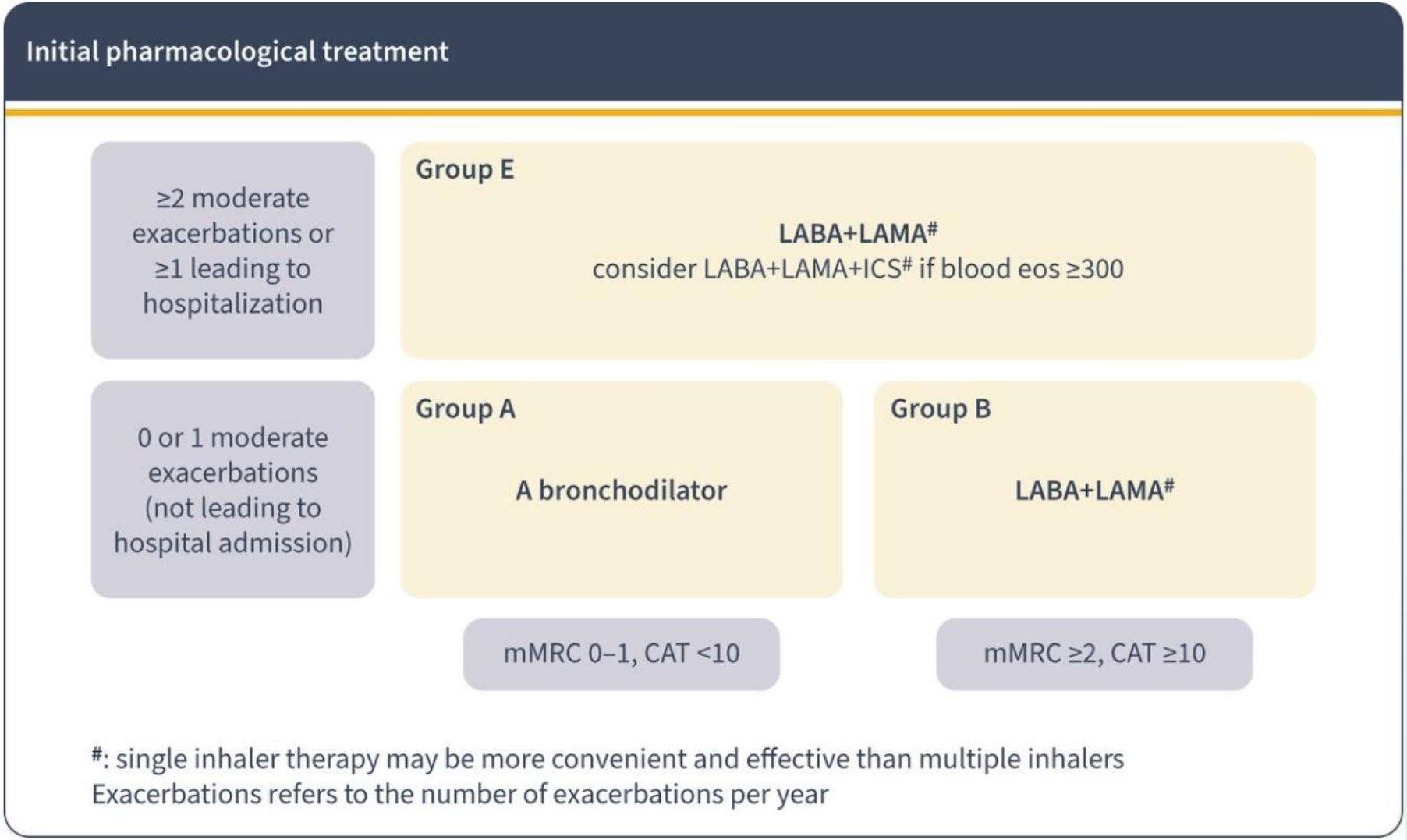
CONSIDER the diagnosis in ANY patient with dyspnoea, chronic cough or sputum production, recurrent wheeze, recurrent chest infections, and exposure to risk factors

Spirometry is MANDATORY showing post bronchodilator OBSTRUCTION with **FEV**

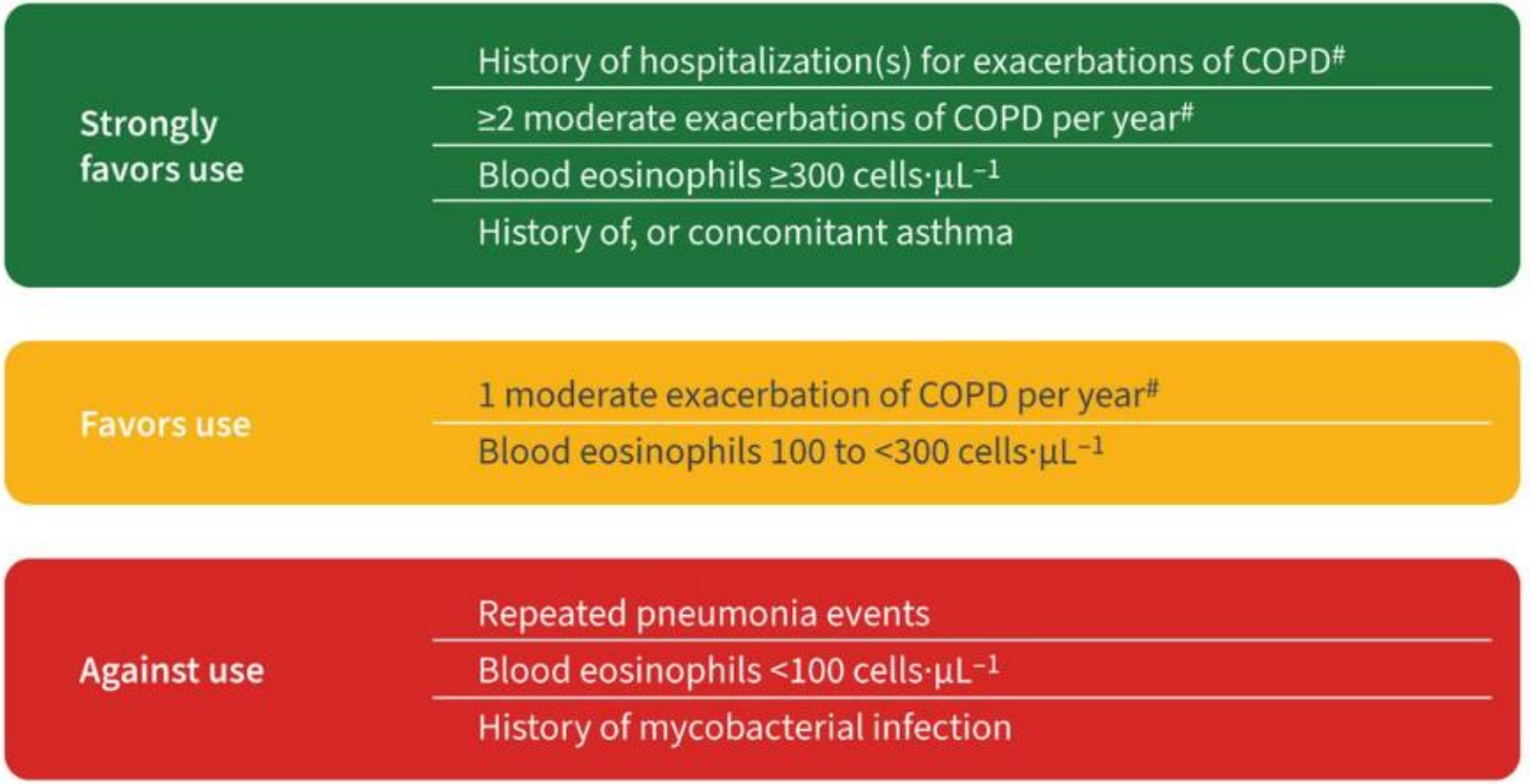


GOLD ABE Assessment Tool



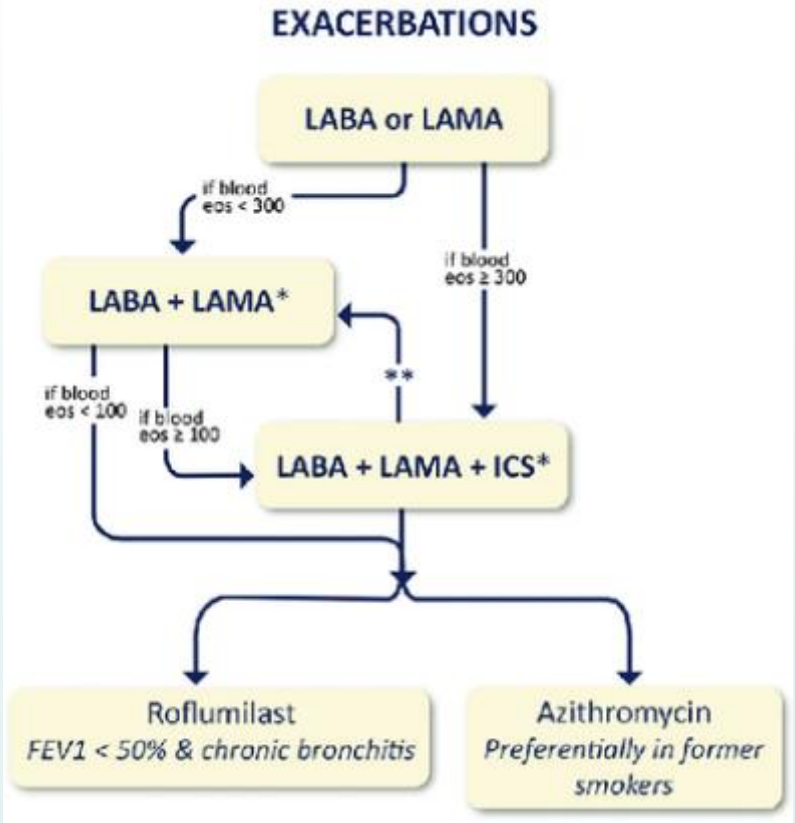

Initial pharmacological treatment
≥2 moderate exacerbations or ≥1 leading to hospitalization
Group E
LABA+LAMA#
consider LABA+LAMA+ICS# if blood eos ≥300
0 or 1 moderate exacerbations (not leading to hospital admission)
Group A
A bronchodilator
Group B
LABA+LAMA#
mMRC 0–1, CAT <10
mMRC ≥2, CAT ≥10
#: single inhaler therapy may be more convenient and effective than multiple inhalers
Exacerbations refers to the number of exacerbations per year

When to add ICS?



#: despite appropriate long-acting bronchodilator maintenance therapy (see Figure 4 and GOLD report Table 3.4 for recommendations). Note that blood eosinophils should be seen as a continuum; quoted values represent approximate cut-points; eosinophil counts are likely to fluctuate.

Add on therapies - recurrent exacerbations



Comorbidities in COPD

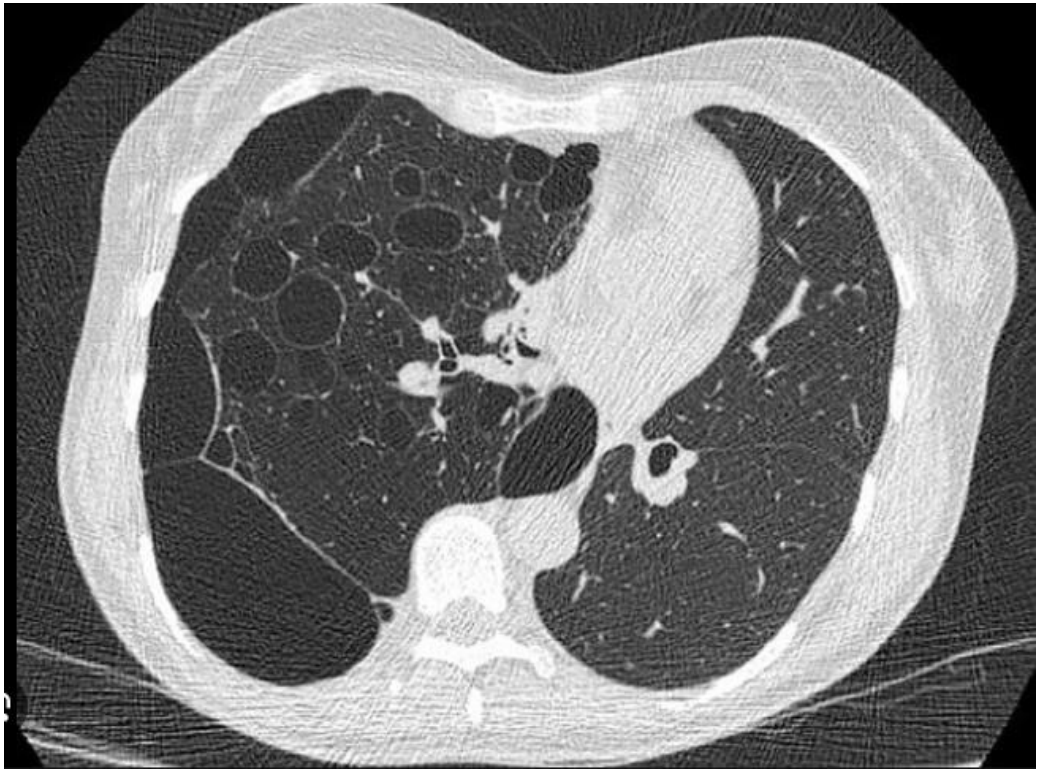
- **Lung cancer**
  - Lung cancer occurs frequently in patients with COPD [**165**]. Like the general population, annual low-dose CT scan is recommended for lung cancer screening in COPD due to smoking
- **Cardiovascular diseases**
  - Common in COPD, their prevalence ranging from 20 to 70%
- **Bronchiectasis**
  - Bronchiectasis affects approximately 30% of patients with COPD
- **Sleep apnea**
  - Sleep apnea occurs in approximately 14% of COPD patients
- **Osteoporosis**
  - Osteoporosis in COPD is often under-diagnosed and associated with poor health status and prognosis. Recurrent use of systemic corticosteroids increases the risk of osteoporosis and should be avoided if possible.

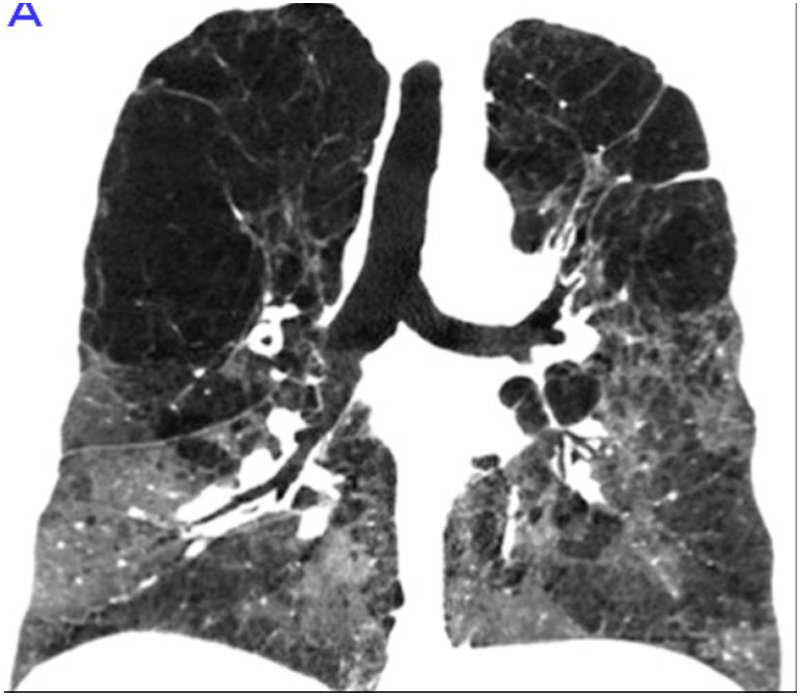
Comorbidities in COPD

- **Diabetes and metabolic syndrome**
  - Studies show that diabetes is more frequent in COPD and the latter is likely to affect prognosis. The prevalence of metabolic syndrome has been estimated to be more than 30%
- **Gastroesophageal reflux**
  - Gastroesophageal reflux (GERD) is an independent risk factor for exacerbations and is associated with worse health status
- **Secondary polycythemia**
  - Secondary polycythemia may be associated with pulmonary hypertension, venous thromboembolism and mortality.
- **Mental health**
  - Anxiety and depression are important and under-diagnosed comorbidities in COPD

Press Release: Dupixent® demonstrates potential to become first biologic to treat COPD by showing significant reduction in exacerbations in pivotal trial

March 23, 2023




A

Surgical and bronchoscopic management

Bullectomy

LVRS (Lung volume reduction surgery)

Endobronchial valves

Endobronchial coils

Vapor ablation

Lung transplantation

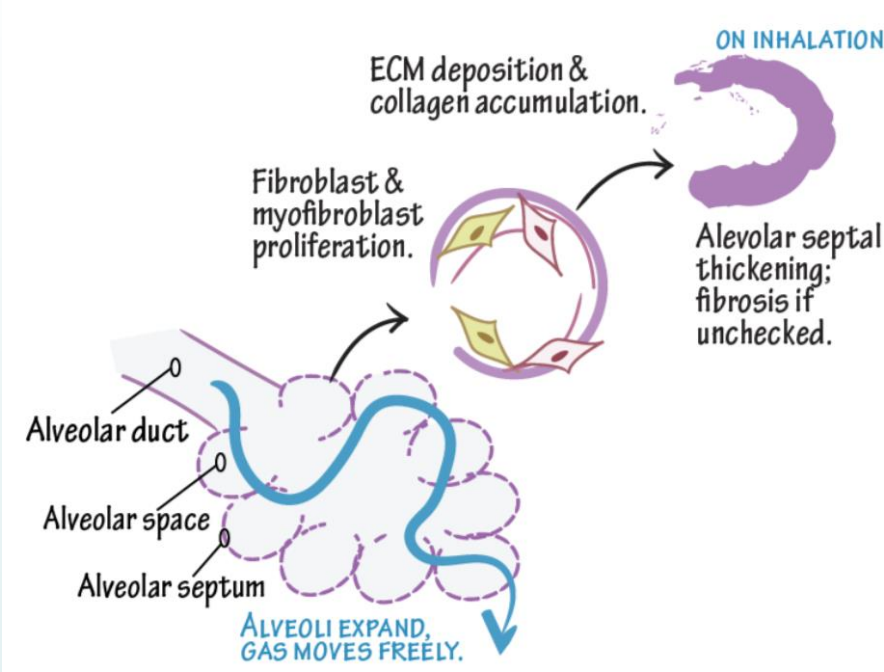
GOLD surgical recommendations

Intervention Bronchoscopy and Surgery	• Lung volume reduction surgery should be considered in selected patients with upper-lobe emphysema **(Evidence A)** • In selected patients with a large bulla surgical bullectomy may be considered **(Evidence C)** • In select patients with advanced emphysema, bronchoscopic interventions reduce end-expiratory lung volume and improve exercise tolerance, quality of life and lung function at 6-12 months following treatment. Endobronchial valves **(Evidence A)**; Lung coils **(Evidence B)**; Vapor ablation **(Evidence B)** • In patients with very severe COPD (progressive disease, BODE score of 7 to 10, and not candidate for lung volume reduction) lung transplantation may be considered for referral with at least one of the following: (1) history of hospitalization for exacerbation associated with acute hypercapnia (Pco_2 > 50 mmHg); (2) pulmonary hypertension and/or cor pulmonale, despite oxygen therapy; or (3) FEV1 < 20% and either DLco < 20% or homogenous distribution of emphysema **(Evidence C)**

ILD

Interstitial Lung diseases

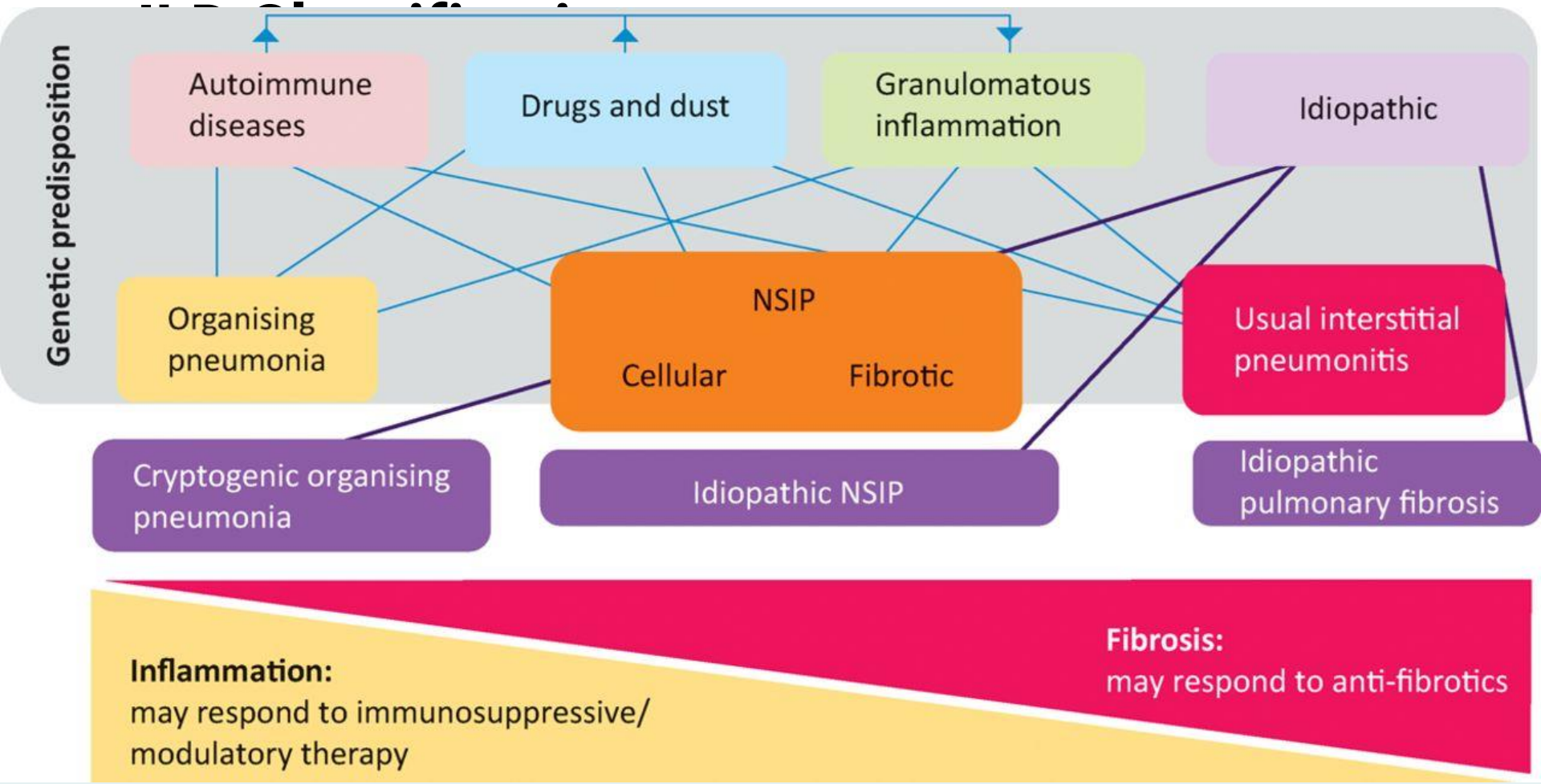
- Umbrella term to describe a wide range of condition that result in lung inflammation and/or scarring
    - Classified into different groups according to underlying cause/radiology/associations
    - Over 300 distinct aetiologies



ILD

- Associated with significant morbidity and mortality
- Heterogeneous and variable progression
- Can progress despite treatment to respiratory failure and death

ILD Classifications


Genetic predisposition
Autoimmune diseases
Drugs and dust
Granulomatous inflammation
Idiopathic
Organising pneumonia
NSIP
Cellular
Fibrotic
Usual interstitial pneumonitis
Cryptogenic organising pneumonia
Idiopathic NSIP
Idiopathic pulmonary fibrosis
Inflammation:
may respond to immunosuppressive/ modulatory therapy
Fibrosis:
may respond to anti-fibrotics

- Ideal management via MDT approach - respiratory physician, radiologist, pathologist and others especially rheumatologist and cardiologist

Drugs and Exposures

Drugs

Nitrofurantoin
Amiodarone
Methotrexate
Chemo e.g. Bleomycin

Organic

Birds
Hay
Mold
Mycobacteria

Inorganic

Asbestos
Silica
Beryllium
Coal dust

History and examination

- **History:** Timeline of events, Main symptoms (commonly breathlessness on exertion insidious onset and dry cough) Risk factors: smoking, occupation, hobbies, pets. Associated symptoms: e.g. joint pains, rashes, dry eyes, dry mouth, Raynaud's phenomenon
    - Classify breathlessness with scale e.g. MRC Dyspnoea scale
- **Examination**: FIne inspiratory crackles, finger clubbing, hypoxaemia (remember to check after mobilising), synovitis, skin changes (e.g. erythema nodosum), joint changes.

Investigations in ILD- the bottom line

Imaging: High resolution CT thorax - key to identify pattern of lung disease

Lung function testing: Spirometry, Lung volumes, Gas transfer

Blood tests including autoimmune screen + optional others: serum ACE, Avian/Aspergillus precipitins, CK

Bronchoscopy - may be useful for differential cell counts esp in NSIP to determine if steroids/immunosuppression appropriate

Lung biopsy - to be judiciously used. AVOID in those with history/exam/radiology suggestive of IPF

Echocardiogram: Assessment of right heart strain/pulmonary hypertension

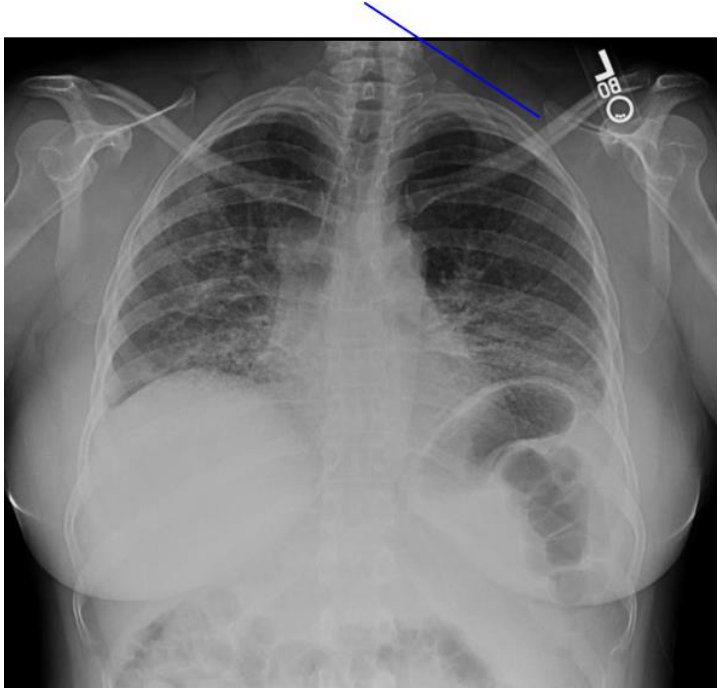
IPF (Idiopathic Pulmonary Fibrosis)

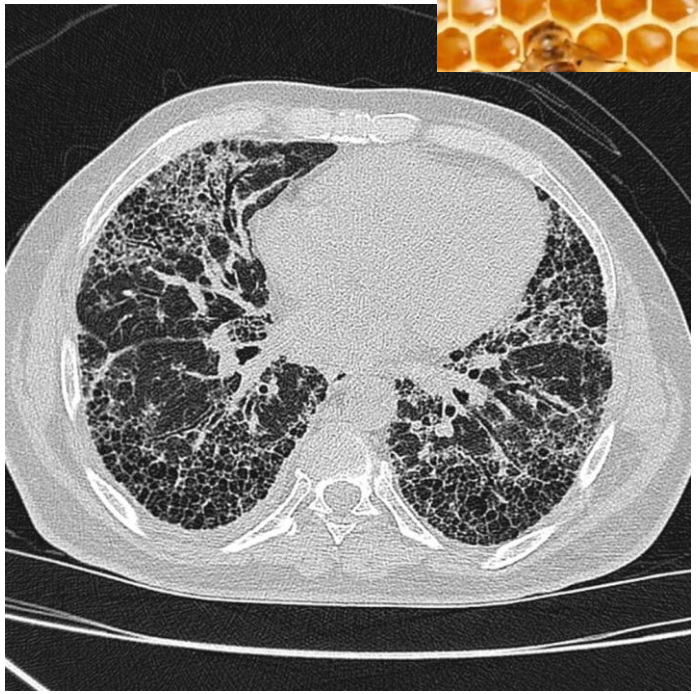
1. The ATS/ERS classification defines IPF as “a specific form of chronic fibrosing interstitial pneumonia of unknown aetiology, limited to the lung and associated with the histological entity of usual interstitial pneumonia”

    a. Pathogenesis factors: **Cellular senescence and micro injuries** due to environmental exposure (to metal, wood dust, stone, sand and silica, working in agriculture and farming), lifestyle (current or a history of smoking), microbial agent infections and a predisposed genetic background

1. Predominantly affects older males (85% diagnoses made in patients >70)
2. Rare disease - Incidence of 12 per 100000 in UK in 2012, No local stats available
3. Typical presentation: Slowly worsening SoB and cough - potentially uncovered following an infection
4. Poor prognosis: 50% of patients with IPF die within 3 years of diagnosis; 20% live >5 years post diagnosis
5. No cure and limited treatment available in context of irreversible loss of lung function

Imaging





Radiological features of IPF

A definite UIP pattern on HRCT is present if the following four radiological criteria are met:

1) subpleural basal predominance

2) reticular abnormality

3) honeycombing with or without traction bronchiectasis (also known as secondary bronchial dilatation)

4) absence of features listed as inconsistent with UIP pattern.

Differentials of UIP radiology

1. Asbestosis - Radiologically the same - i.e. UIP pattern of fibrosis. Diagnosis mainly based on detailed occupational history

1. Connective tissue disease related ILD (predominantly rheumatoid arthritis) - May precede joint symptoms

Evolvement in management of IPF

1. Historically, management of IPF primarily involved immunosuppression using a combination therapy with prednisolone, azathioprine and N-acetylcysteine

    a. Landmark PANTHER study in 2012 highlighted that this regimen was associated with poor outcomes in comparison with placebo

1. Focus now on coining diagnosis early and starting antifibrotic therapy early alongside pulmonary rehabilitation, oxygen therapy if needed and palliation of symptoms

1. Lung transplantation an option in few patients

Antifibrotic therapy for mild to moderate IPF - NICE Guidelines

Pirfenidone and Nintedanib are recommended as an option for treating idiopathic pulmonary fibrosis in adults only if:

a. the person has a forced vital capacity (FVC) between 50% and 80% predicted

a. treatment is stopped if there is evidence of disease progression (an absolute decline of 10% or more in predicted FVC within any 12 month period).

Antifibrotics - underlying evidence

- The clinical efficacy of pirfenidone (ESBRIET) is supported by a Cochrane meta-analysis of three phase III studies (i.e. the Japanese SP3 trial and the two phase III CAPACITY studies), which demonstrated that **treatment with pirfenidone reduced the risk of disease progression or death by 30%** (HR 0.70, 95% CI 0.56–0.88; p = 0.002)

- Pooled analysis of data from three 52-week trials with OFEV® (nintedanib), INPULSIS®-1, INPULSIS®-2 and TOMORROW, including 1231 patients with IPF showed **50% relative reduction in annual rate of decline of FVC**

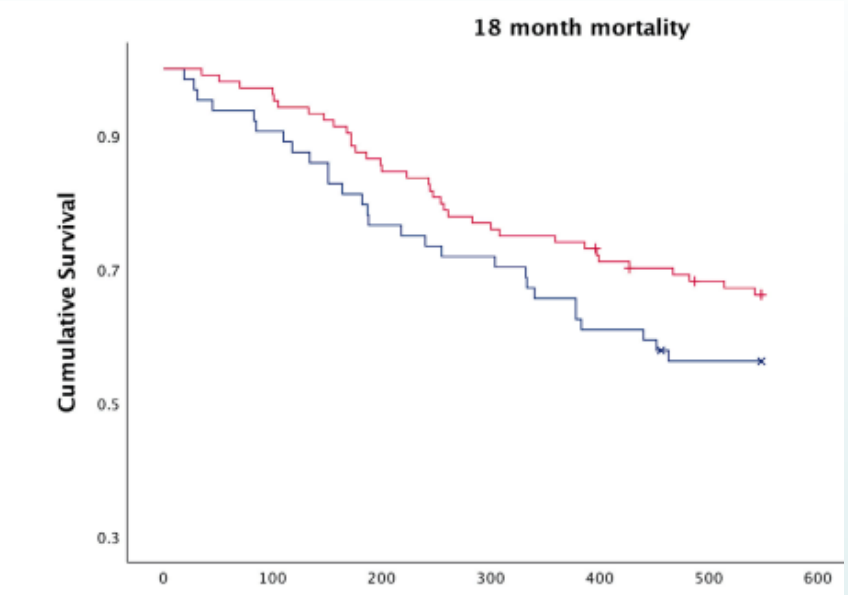
**strict inclusion criteria of only mild to moderate disease severity and excluding multiple comorbidities*

Side effect profile

- Nintedanib
  - GI disturbances - diarrhoea often problematic (62% experienced it during study) - patients usually prescribed loperamide
  - Derangement of LFTs
- Pirfenidone
  - GI disurbances - diarrhoea not so prominent, loss of appetite can be a major issue
  - Photosensitivity - patients usually prescribed sun factor
  - Derangement of LFTs
  - Upper resp tract infections

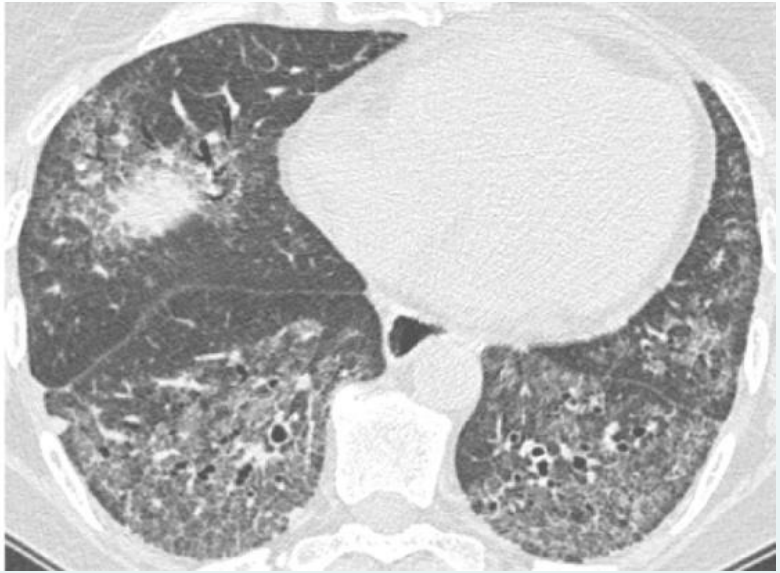
Real-world retrospective observational study exploring the effectiveness and safety of antifibrotics in idiopathic pulmonary fibrosis - 2021

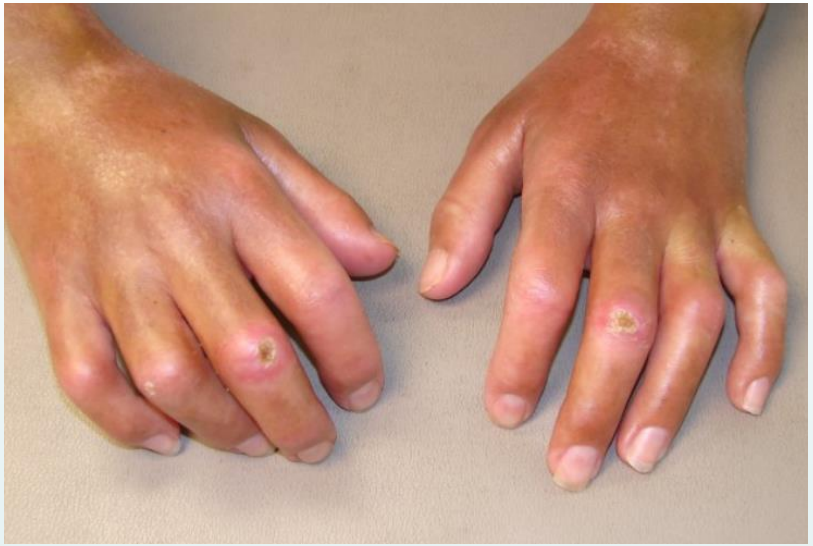
1. Antifibrotics are having promising effects on progression-free survival, lung function and mortality.
2. Nintedanib appears better tolerated than pirfenidone in the early stages of antifibrotic therapy.
3. The lower rates of treatment discontinuation for patients treated with nintedanib may have positive outcomes on mortality.



ILD	Treatment options	Status/Evidence	References
IPF	Nintedanib	FDA approved	1
	Pirfenidone	FDA approved	1
	Recombinant human pentraxin 2 (rhPTX-2; PRM-151)	Phase 3 Terminated due to futility NCT04552899 NCT04594707	2
	Pamrevlumab (FG-3019)	Phase 3 Recruiting NCT03955146 NCT04419558	3
	Autotaxin inhibitor (Ziritaxestat)	Phase 3 Completed NCT03733444 NCT03711162	4
	PDE4B inhibitor (BI 1015550)	Phase 2 Completed NCT04419506	5
	Anti-androgen (Danazol)	Phase 2 Recruiting NCT04638517 TELOSCOPE study	6
	TD139-Gal-3 inhibitor	Phase 2 Recruiting NCT03832946	7
	BMS-986278-LPAR1 inhibitor	Phase 2 Recruiting NCT04308681	8
	Saracatinib	Phase 1b/2a Recruiting NCT04598919	9
	Senolytics (Dasatinib plus Quercetin)	Phase 1 Completed NCT02874989	10
	Autologous lung stem cells	Phase 1 Recruiting NCT04262167 NCT02745184	10
	tRNA synthetase inhibitor	Phase 1 Recruiting NCT03711162 NCT04888715	10
	TRK-250-TGFβ1 suppression (inhaled)	Phase 1 Recruiting NCT03727802	10

Spot diagnosis?





SSc ILD (Systemic Sclerosis ILD)

- One of the main causes of death in SSc (Pulmonary hypertension is the other)
  - Affects mainly those with diffuse disease (85-90% pick up on CT)
  - Anti Scl 70 positivity = higher risk of ILD
  - Important to screen clinically and do lung function tests for early detection as ILD is asymptomatic for a long time
  - Subtype: NSIP (around 75%)

Interstitial lung disease and autoimmunity

Recognised pathologies:

- Rheumatoid arthritis
- Scleroderma or systemic sclerosis
- Sjogren's syndrome
- Systemic lupus erythematosus
- Polymyositis and Dermatomyositis
- Mixed connective tissue disease
- Undifferentiated connective tissue disease

,

RA-ILD

60 % of pts. but clinically symptomatic in 5-10% of the pts

Main preventable risk factor is smoking(>25 pack years 3.1 fold increase)

Male gender 2-3 times more likely

Genetics MHC region , MUC5b gene & RA-ILD

Severe arthritic features

Higher titres of Anti CCP antibodies and Rheumatoid factor

Lung manifestation can precede joint issues

Phenotypes

Pattern	Radiology	Prevalence	Prognosis
UIP pattern	minimal GGO, basal , subpleural reticulation and honeycombing(HC) with tractional bronchodilation	8-66%	Worst outcome
NSIP pattern	Extensive GGO ,basal , subpleural sparing , some tractional bronchodilation , no HC	19-57%	Better then UIP
Organising pneumonia	focal GGO , consolidation ,subpleural and peribronchial, reversed halo sign	0-11%	Good outcomes
Others (LIP or DIP)	GGO , cysts, centrilobular nodules , upper lobe predominant , peribronchovascular septal thickening	<1%	
CPFE	Coexistant Emphysema , 50% of patients with smoking history who have got RA-ILD		

SARD-ILD: FIRST-LINE TREATMENT

	Preferred	Additional Options
Systemic Sclerosis (SSc)	Mycophenolate Tocilizumab Rituximab	Cyclophosphamide Nintedanib Azathioprine
Myositis	Mycophenolate Azathioprine Rituximab CNI	JAKi Cyclophosphamide
MCTD	Mycophenolate Azathioprine Rituximab	Tocilizumab Cyclophosphamide
Rheumatoid Arthritis (RA)	Mycophenolate Azathioprine Rituximab	Cyclophosphamide
Sjögren's	Mycophenolate Azathioprine Rituximab	Cyclophosphamide

AVOID GC X

+ short-term GCs (Glucocorticoids)+

X SSc ILD: strong Recommendation against glucocorticoids as first-line treatment

+ Use GCs cautiously in patients w/ MCTD with SSc phenotype (↑ risk of renal crisis)

SCREENING & MONITORING for ILD

↑ Risk for ILD → PFTs + HRCT Chest

S/Sx of ILD → PFTs + HRCT Chest

- PFT: spirometry, lung volumes, and diffusion capacity
- HRCT = High Resolution CT

Monitoring Tests

(+) ILD Diagnosis:

PFTs
- IIM: q3-6mo x 1st yr*
- SSc: q3-6 mo x 1st yr*
- RA/SjD/MCTD: q3-12 mo x 1st yr*

Ambulatory **Desat** Testing q3-12mo

HRCT Chest as needed

*then less frequently once stable

Adapted from ACR Guidelines (2023)

SARD-ILD: PROGRESSION Despite First-Line ILD Treatment

	Add (OR) Switch Treatments:	
Systemic Sclerosis (SSc)	Mycophenolate Rituximab Nintedanib	Tocilizumab Cyclophosphamide AHSCT referral
Myositis	Mycophenolate Rituximab CNI Nintedanib	Cyclophosphamide IVIG JAKi
MCTD	Mycophenolate Rituximab Nintedanib	Tocilizumab Cyclophosphamide IVIG
Rheumatoid Arthritis (RA)	Mycophenolate Rituximab Nintedanib	Tocilizumab Cyclophosphamide Pirfenidone
Sjögren's	Mycophenolate Rituximab	Nintedanib Cyclophosphamide

Against Long-Term Glucocorticoids X

Referral for Lung Transplant Evaluation as Appropriate

SARD with RAPIDLY PROGRESSIVE ILD (RP-ILD)

RP-ILD → Severe Disease (or) Confirmed or Suspected anti-MDA5

MDA5 (or) Severe Disease → Yes / No

Triple Therapy:
IV Glucocortioids
+
2 Additional Rx

Rituximab
Cyclophosphamide
IVIG •
Mycophenolate
Calcineurin Inhibitor
JAKi

Other RP-ILD → IV Glucocortioids + 1-2 Additional Rx

* RTX/CYC recommended over IVIG

Consider Early **Lung Transplant** Referral

Management in ILD

- Antifibrotics and/or Anti-inflammatory modalities
- Smoking cessation
- Pulmonary rehabilitation
- Vaccination - Flu/Pneumococcal
- Inhaled therapy in those with concomitant COPD/Asthma
- Oxygen therapy (ideally guided by blood gases)
- Palliative care
- PDE5 inhibitor in secondary pulmonary hypertension associated with IPF
- Lung transplantation is NOT a realistic option for our patients currently
- **Monitor disease progression and adjust therapies**

Summary

Respiratory pathologies exhibit similar symptoms - important to ascertain exact pathology to initiate appropriate treatment

Eosinophil key marker of inflammation in asthma and COPD - remember to check!

Immunotherapies hopefully available locally for severely ill patients

Imaging, bloods and lung function testing paramount in ILD. Antifibrotic therapies more readily available.

Thank you, any questions?