DRUG INDUCED ILD

Dr Jayabharathi Palanivel

QUESTION 1

ILD -Drug induced or not ?

QUESTION 2

Investigation of choice ?

QUESTION 3

What next ?

Discontinue drug ?
Steroid ?

KEY MILESTONE OF DRUG INDUCED PULMONARY TOXICITY

1st report -19th century by William Osler-

Opiates causing Pulmonary disease

1972

Bleomycin – Pulmonary fibrosis

1st recognition of drug induced ILD

1997

PNEUMOTOX database to track Drug induced respiratory diseases

2010's- present

> 400 drugs identified

Impact of Targeted therapies EGFRI and ICI

PNEUMOTOX
ON LINE

The Drug-Induced Respiratory Disease App

Philippe Camus, M.D.
Dijon, France

Supported by a Grant from the ERS

Version : 2.2 / Mobile

PNEUMOTOX
ON LINE
v2.2

The Drug-Induced Respiratory Disease Website

Philippe Camus, M.D.
Dijon, France

Search by » KEYWORD DRUG / PATTERN

DIAGNOSING DIRD

Search results :

Drugs 4 | Patterns 9 | Publications 169 | Medias 0

Amiodarone — 5

I.a I.b I.c I.d I.e I.f I.g I.h I.k I.l I.s I.u
I.w I.z I.aa I.ao I.at I.ax I.ay II.b II.l III.a
IV.d IV.r V.a V.c V.d V.t VI.a VI.i VIII.a IX.a
X.d X.f X.q XI.c XI.f XI.bq XII.a XII.c XII.e XII.l
XII.t XII.af XII.au XV.a XV.b XV.c XV.d XV.f XV.g XV.h
XV.k XV.m XV.o XV.r XV.ao XV.bt XVI.b XVI.i XVI.j XVI.n XVI.s XVI.w
XVI.aa XVI.ab XVI.ay XVI.az XVI.bj XVI.bq XVI.bt XVI.bx XVII.e XVIII.b XVIII.j XVIII.k
XVIII.p XIX.a XIX.b XIX.c XIX.e XIX.f XIX.m XIX.p

I - Interstitial/parenchymal lung disease
I.l - Diffuse alveolar damage (DAD) (see alsoo under IIb and XVf)

Amiodarone, i.v. — 1

I.at VI.a VI.i X.f

Dronedarone — 2

I.a I.b I.d I.l II.b XII.a XII.t XV.c XV.f

Oxygen (dioxygen, O2) — 4

I.l I.v II.a II.b VIII.d VIII.k IX.p XI.b XI.e XV.f XV.h XVI.bj
XIX.b

Search results :

Drugs 4 | Patterns 9 | Publications 169 | Medias 0

I - INTERSTITIAL/PARENCHYMAL LUNG DISEASE

I.g - Pulmonary fibrosis	88
I.k - Lung nodule or nodules	22
I.u - Relapsing or migrating pneumonitis/pneumonia (see also Id)	7
I.at - Amiodarone pulmonary toxicity - Amiodarone lung	2

II - PULMONARY EDEMA - ACUTE LUNG INJURY - ARDS

II.b - ARDS - Acute lung injury	281

IV - AIRWAY INVOLVEMENT

IV.d - Cough (lone)	65

XV - PATHOLOGY

XV.r - Path: Smudged geographic necrosis	1

XVI - IMAGING

XVI.z - Imaging: A large nodule or a mass	2

XVIII - DISTINCTIVE PATTERNS - 'EYE-CATCHERS'

Search results :

Drugs 4 | Patterns 9 | Publications 169 | Medias 0

"White Thyroid" on Unenhanced Computed Tomography in Amiodarone-Induced Thyrotoxicosis Type 2.
VAN DEN BRUEL A, DELANOTE J, BRAECKMAN A, DE VROE C, PYFFEROEN L, GHEKIERE J, DUYTSCHAEVER M, TAVERNIER R
Thyroid : official journal of the American Thyroid Association 2018 Jun;28;769-772 2018 Jun

[Amiodarone pulmonary toxicity: radiological coexistence of nodules with interstitial and alveolar abnormalities].
DE GRANDA ORIVE JI, HERRERA DE LA ROSA A, MARTÍNEZ ALBIACH JM, ESCOBAR SACRISTÁN JA, SÁEZ VALLS R, GALLEGO RODRÍGUEZ V
Anales de medicina interna (Madrid, Spain : 1984) 1998 May;15;267-9 1998 May

[Amiodarone-induced pneumonitis associated with marked eosinophilia in BALF].
SATO S, WATANABE K, ISHIDA T, YOSHIKAWA M, KANAZAWA K, SAITO J, OHTSUKA Y, SUZUKI H, MARUYAMA Y, MUNAKATA M
Nihon Naika Gakkai zasshi. The Journal of the Japanese Society of Internal Medicine 2006 Feb 10;95;356-8 2006 Feb 10

[Amiodarone-induced pneumonitis. Lethal complication in a patient after thoracic surgery].
GHEZEL-AHMADI V, KÜRSCHNER VC, FISSELER-ECKHOFF A, SCHIRREN J, SCHMITZ JE, OBENHAUS T
Der Anaesthesist 2008 Oct;57;982-7 2008 Oct

[Amiodarone-induced segmental lung infiltration. Radiologic and computed tomographic aspects].
FRIEDRICH M, HOFFMANN E, MITLEHNER W

Search results :

Effects 4

BLEOMYCIN

I.b - Pneumonitis (ILD)	4
I.c - Eosinophilic pneumonia (pulmonary infiltrates and eosinophilia)	1
I.g - Pulmonary fibrosis	2
XVI.e - Imaging: Pulmonary opacities with a subpleural distribution	2

CISPLATIN

I.c - Eosinophilic pneumonia (pulmonary infiltrates and eosinophilia)	1

GEFITINIB

I.b - Pneumonitis (ILD)	5
I.g - Pulmonary fibrosis	1
XIX.c - BAL: An excess proportion of eosinophils	1

PEMETREXED

I.b - Pneumonitis (ILD)	3

FREQUENCY ?

- \- Questionable signal
- 1 < 10 cases
- 2 10 - 50 cases
- 3 50 - 100 cases
- 4 100 - 200 cases
- 5 >200 cases

PNEUMOTOX.COM

DRUG SEARCH

DRUG INDUCED LUNG INJURY - DEFINTION

- Heterogeneous group of adverse drug reactions, ranging from mild to progressive and life-threatening disease

- Affects the airway, parenchyma, pulmonary vessels, and pleura.

Camus P, Bonniaud P, Fanton A, et al. (2004) Drug-induced and iatrogenic infiltrative lung disease. Clin Chest Med

GENERAL PRINCIPLES OF DILI

- Clinical presentation : non-specific
- Variable latency from drug initiation
- Often dose independent
- May be acute, subacute or chronic
- Variety of radiographic and histopathologic pattern
- Diagnosis of exclusion
- Resolution usually occurs with discontinuation and rechallenge is generally not recommended

Megan Harrison.et.al (2024)Drug-induced interstitial lung disease: Expert Review of Respiratory Medicine, 18

CONTRIBUTING CONFOUNDING FACTORS

- Non-specificity of clinical, radiological and histological findings
- Multiple pulmonary manifestations for a single drug
- Compounded toxicity with multiple drugs
- Underlying disease with similar pulmonary manifestation
- Idiosyncratic in majority of cases (dose- independant)

  Exceptions (amiodarone, bleomycin.)

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EPIDEMIOLOGY

Drug/Class	Number of Studies	Quality	Study Design	Patient Population	Sample Size (Range)	Case Definition of DIILD	Estimated Incidence (Range)	Estimated Mortality in Those with DIILD (Range)
Cancer Therapies								
Bleomycin [18–24]	7	Moderate = 3 Low = 3 Very low = 1	Meta-analysis = 2 Observational studies = 5	Various cancers (1 meta-analysis in ovarian sex cord stromal tumours and 1 in all cancer RCT data)	22–1147	variable	Meta-analyses: 6.8–15% Other studies: 6.8–21%	Meta-analyses: 8.1–23% Other studies: 0–48%
Gemcitabine [13,25–32]	9	Moderate = 2 Low = 6 Very low = 1	Meta-analysis = 2 Clinical trial = 3 Observational = 4	Cancer (predominantly pancreatic and non-small cell lung cancer but also others)	Meta-analysis: 1308–1742 Others: 26–2440	variable	1.1–3.9%	0–22%
Epidermal growth factor receptor-targeted therapies (EGFR)								
Erlotinib [34–36,89,90]	5	Moderate = 2 Low = 3	Meta-analysis = 2 Post marketing surveillance = 2 Observational = 1	Non-small cell lung cancer	341–9909	variable	0.9–5.9%	31–45%
Gefitinib [34–37]	4	Moderate = 2 Low = 2	Meta-analysis = 2 Post marketing surveillance = 2	Non-small cell lung, breast and colorectal cancer	70–5468	variable	1.9–3.5%	18–44%
Panitumumab [33,39]	2 (but reporting from same cohort)	Moderate = 2	Post marketing surveillance	Colorectal cancer	3085	Expert case review	1.3%	51.3%
Cetuximab [38]	1	Moderate = 3	Post marketing surveillance	Colorectal cancer	2006	Physician reported	1.2%	41.6%
Mechanistic target of rapamycin protein (MTOR) inhibitors								
Everolimus [40–43,45,46,48,49]	8	Moderate = 3 Low = 3 Very low = 2	Meta-analysis = 1 Clinical trial = 2 (same trial 2 separate published analyses) Observational = 5	Neuroendocrine cancer Renal cell cancer Renal transplant	40–2261	Variable, including radiographic signs of DIILD	2.8–58%	5.4–20%
Temsirolimus [44,47]	2	Low = 2	Meta-analysis = 1 Clinical trial = 1 Observational study = 1	Neuroendocrine cancer Endometrial cancer Renal cell cancer	22–408	Variable	29–36%	n/a
Sirolimus [48]	1	Very low = 1	Observational	Renal/pancreas transplant	115	Physician reported	9.5%	0%
Check point inhibitors (CPI)								
All CPIs [51–53]	3	High = 2 Moderate = 1	Meta-analysis = 2 Observational = 1	Non-small cell lung cancer	1826–3232	variable	1.1–3.6%	8–9.4%

Skeoch S. et al. Drug Induced Interstitial Lung Disease: A Systematic Review. J Clin Med. 2018.

Drug/Class	Number of Studies	Quality	Study Design	Patient Population	Sample Size (Range)	Case Definition of DIILD	Estimated Incidence (Range)	Estimated Mortality in Those with DIILD (Range)
Ipilimumab [91]		Low = 1	Observational = 1	Melanoma	146	Radiographic evidence of DIILD	5.44%	n/a
Nivolumab [92]	1	Low = 1	Post hoc pooled clinical trial analysis = 1	Cancer (various types)	170	Physician reported events	11.7%	0%
Other agents identified								
Irinotecan [93]	1	Low = 1	Post marketing surveillance	Cancer (various types)	8864	Physician reported	0.74%	24%
Rituximab [67,72–74]	4	Very low = 4	Systematic reviews = 3 Case series = 1	Predominantly cancer but other indications included	16–52	Variable	n/a	n/a
Imatinib [94]	1	Low = 1	Post marketing surveillance	Leukaemia	6	Physician reported	n/a	6/6 resolved
Pemetrexed [95]	1	Moderate = 1	Post marketing surveillance	Mesothelioma Non-small cell lung cancer	903	Expert committee review	1.8%	
Granulocyte colony stimulating factor [96]	1	Low = 1	Observational	In conjunction with chemotherapy	40 treated vs. 25 with chemotherapy along	Physician reported	0.2% vs. 0% in the control group	n/a
Rheumatology drugs								
Methotrexate [55–61,67]	8	Moderate = 3 Low = 4 Very low = 1	Meta-analysis = 2 Clinical trial = 3 Observational = 2 Case series = 1	Rheumatoid arthritis Psoriasis, psoriatic arthritis or inflammatory bowel Primary biliary cirrhosis	29–3188	variable	0.06–15%	10–33%
Tumour necrosis factor inhibitors [67–72,97,98]	8	Moderate = 4 Low = 1 Very low = 3	Post marketing surveillance = 3 (2 papers report on 1 study) Observational study = 3 Systematic review of case reports = 3	Predominantly rheumatoid arthritis but cases in other diseases	233–13,894	variable	0.6%	32%
Leflunomide [62–66]	5	Moderate = 1 Low = 3 Very low = 1	Meta-analysis of RCTs = 1 Case control via claims database = 1 Post marketing surveillance = 2 Case series = 1	Rheumatoid arthritis	2274–62,734	variable	0–1.2%	19–41%

Skeoch S. et al. Drug Induced Interstitial Lung Disease: A Systematic Review. J Clin Med. 2018.

Drug/Class	Number of Studies	Quality	Study Design	Patient Population	Sample Size (Range)	Case Definition of DIILD	Estimated Incidence (Range)	Estimated Mortality in Those with DIILD (Range)
Cardiology drugs								
Amiodarone [80–88,99–101]	12	Moderate = 2 Low = 5 Very low = 5	Observational = 7 Case series = 5	Cardiovascular disease	13–500	Variable, often not restricted to DIILD	1.2–8.8%	0–41%
Bepridil [102]	1	Low = 1	Observational	Cardiovascular disease	222	Standardised definition	6.3%	0%
Statins [103]	1	Very low = 1	Observational (Adverse events reporting database)	Cardiovascular disease/prevention			1/40 adverse event reports for statins were ILD	n/a
Anti-infection agents								
Nitrofurantoin [75–78,104]	5	Low = 3 Very low = 2	Case-control study = 1 Registry study = 1 Post marketing surveillance = 1 Case series = 2	Chronic and acute treatment of urinary tract infection	10–70,804	Variable, some used "any ILD" after use of drug	3.65%	1.34%
Daptomycin [79,105]	2	Low = 2	Observational study = 1 Post marketing surveillance = 1	Infection (one study specifically infective endocarditis)	58–102	Variable	2.9%	n/a
Interferon [106]	1	Very low = 1	Systematic review of case reports	Hepatitis C	25	Variable	n/a	n/a

Skeoch S. et al. Drug Induced Interstitial Lung Disease: A Systematic Review. J Clin Med. 2018.

PATHOPHYSIOLOGY AND MECHANISM

PATHOPHYSIOLOGY

Idiosyncratic event:

- Seen in majority of cases (often dose independent)

- Risk factors influencing individual's susceptibility:

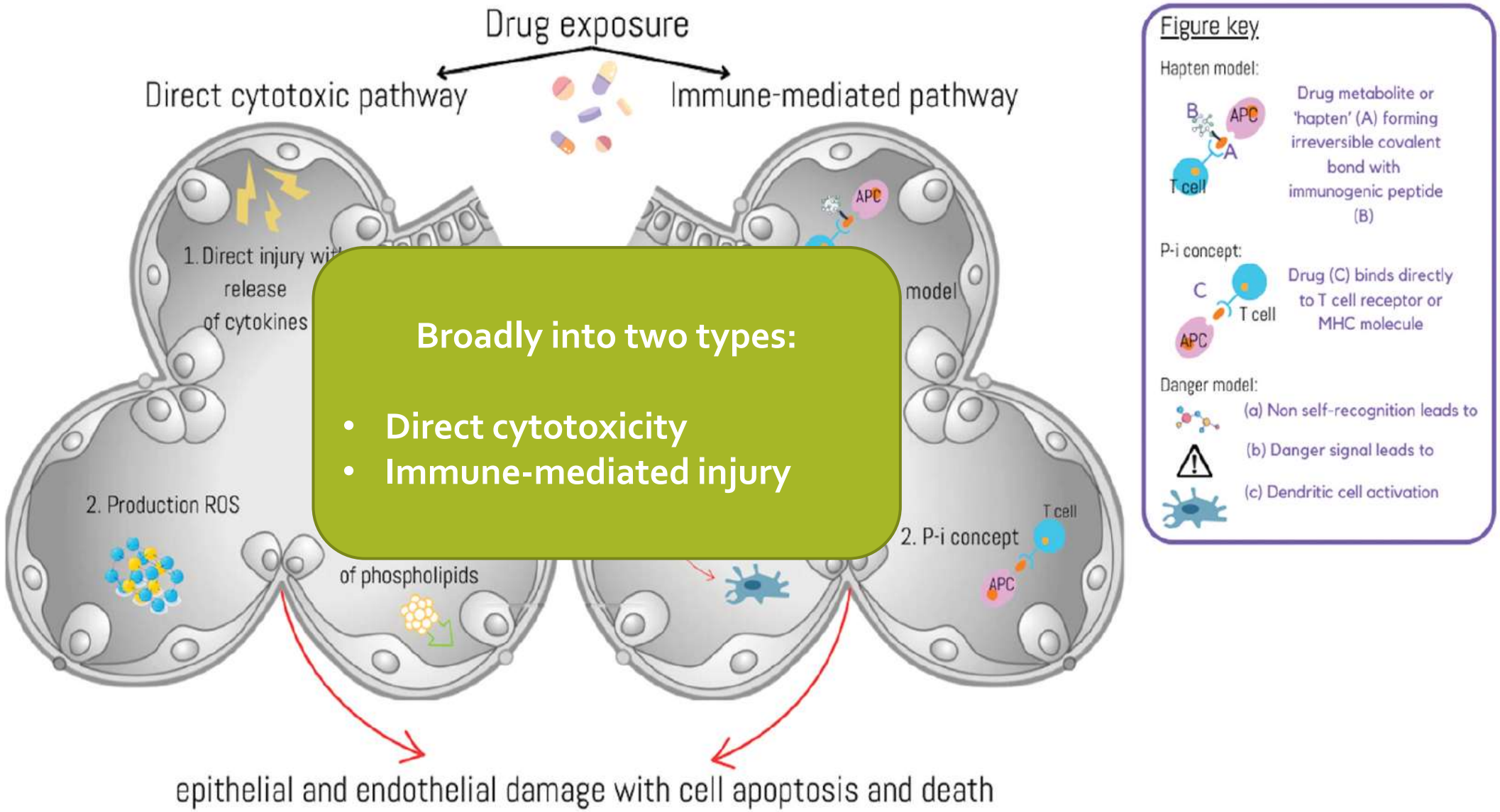
a) Genetically determined

b) Due to concurrent exposures to other medications or environmental agents

c) Individual's comorbid disease

d) Combination of these factors

Delaunois LM. Mechanisms in pulmonary toxicology. Clin Chest Med. 2004



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OTHER MECHANISMS

- Interference with alveolar repair (EGFR inhibitors)
- Abnormal protease/antiprotease balance and interference with lipid metabolism (Amiodarone)
- Oxygen radical generation : Cytotoxic damage (Bleomycin)
- Redox recycling (Nitrofurantoin , paraquat, adriamycin)

Delaunois LM. Mechanisms in pulmonary toxicology. Clin Chest Med. 2004

RISK FACTORS	COMMENTS
Dose-dependent toxicity	• Amiodarone (400mg for at least 2 months) bleomycin (400 units),mitomycin (50 mg·m−2), • Chest radiation therapy.
Underlying condition associated with ILD	• Rheumatoid arthritis • Systemic sclerosis
Combination of pneumo-toxic drugs	Chemotherapies, following radiation and/or ICIs
Genetics	• Familial pulmonary fibrosis • EGFR TKI in Japanese population
High FiO_2	Chemotherapy, radiation, amiodarone
Rechallenge	Usually not recommended and, if needed, only after multidisciplinary discussion.

Spagnolo P, Bonniaud P, Rossi G, et al. Drug-induced interstitial lung disease. Eur Respir J 2022;

CLINICAL FEATURES

- Nonspecific mostly
- Cough
- Fever
- Dyspnea
- Hemoptysis
- Pleuritic chest pain

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GENERAL APPROACH

- High index of suspicion - If there is any temporal association
- Recognition of patterns of lung injury
- Excluding other etiological causes

a)Lab testing

b)CXR and HRCT

c)PFT

d)Echo

e)Bronchoscopy

f)Biopsy

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Category	Tests/Indicators
Total White Cell Count, differential	Blood eosinophilia
Imaging	Chest X-ray, HRCT
Pulmonary Function Tests	Reduced DLCO, FEV1, FVC, and/or TLC
Selected Microbiological Testing	Opportunistic infections • Viral - SARS CoV2, CMV • Fungal -Aspergillosis, Pneumocystis jirovecii • Bacterial - Tuberculosis,NTM, Nocardia species • Parasitic - Strongyloidiasis, Ascariasis, Schistosomiasis

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Category	Tests/Indicators
Bronchoscopy for BAL Cultures and Cell Count Differential	▪ BAL galactomannan ▪ BAL eosinophilia, lymphocytosis ▪ Hemosiderin laden macrophages(alveolar haemorrhage) ▪ Foamy macrophages (amiodarone)
EBUS with Transbronchial Needle Aspiration	Granulomatous inflammation (sarcoidal reaction) versus malignancy
Autoantibodies Including ANCA	ILD secondary to existing or emerging autoimmune disease (RA, SScl, vasculitis, paraneoplastic)
Cardiac Tests (BNP, Troponin, Echo)	Drug-induced or unrelated (cardiogenic pulmonary edema)

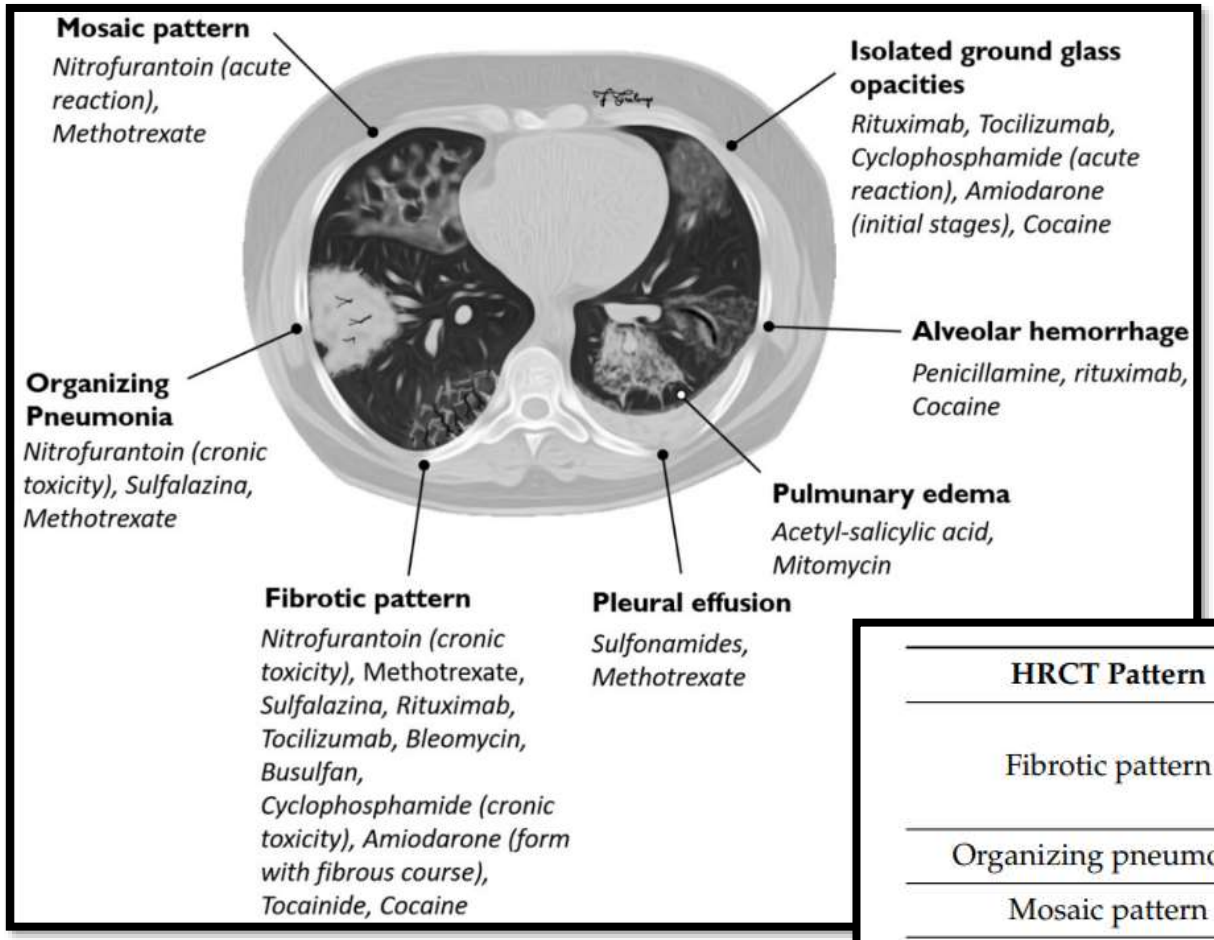
U. Costabel et al. (2004). Bronchoalveolar lavage in drug-induced lung disease. Clinical Chest Medicine.

PATTERNS OF ILD

COMMONEST PATTERN

- Nonspecific interstitial pneumonia (NSIP)
- Organizing pneumonia (OP)
- Hypersensitivity pneumonitis (HP)
- Diffuse alveolar damage (DAD)
- Eosinophilic pneumonia (EP),

Distefano G, Fanzone L, Palermo M, et al. HRCT Patterns of Drug-Induced Interstitial Lung Diseases: A Review. Diagnostics. 2020

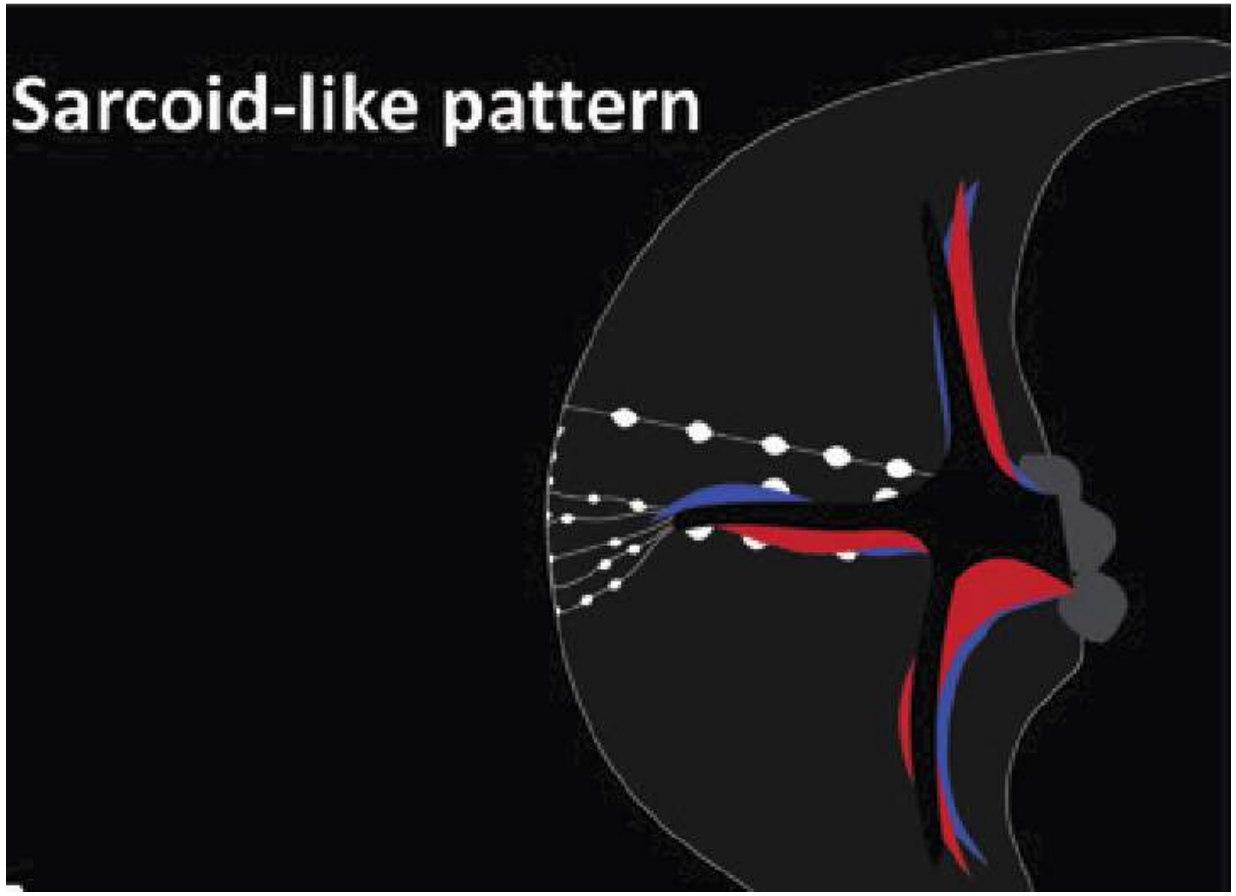


HRCT Pattern	Associated Drugs
Fibrotic pattern	Nitrofurantoin (chronic toxicity), methotrexate, sulfalazina, rituximab, tocilizumab, bleomycin, busulfan, cyclophosphamide (chronic toxicity), amiodarone (form with fibrous course), tocainide, cocaine
Organizing pneumonia	Nitrofurantoin (chronic toxicity), methotrexate
Mosaic pattern	Nitrofurantoin (acute toxicity), methotrexate, sulfalazina
Isolated ground glass	Rituximab, tocilizumab, cyclophosphamide (acute reaction), amiodarone (initial stage), cocaine
Alveolar hemorrhage	Penicillamine, rituximab, cocaine
Pulmonary edema	Acetyl-salicylic acid, mitomycin
Pleural effusion	Sulfonamides, methotrexate

Distefano G, Fanzone L, Palermo M, et al. HRCT Patterns of Drug-Induced Interstitial Lung Diseases: A Review. Diagnostics. 2020

SARCOID LIKE PATTERN

- The pattern is characterized by the presence of sarcoidosis-like bilateral pulmonary infiltrates and non-necrotizing granulomas surrounded by variable signs of fibrosis
- Mediastinal lymphadenopathy
- Drugs : Infliximab and etanercept



Distefano G, Fanzone L, Palermo M, et al. HRCT Patterns of Drug-Induced Interstitial Lung Diseases: A Review. Diagnostics. 2020

RADIOLOGICAL PATTERN AND OTHER PULMONARY MANIFESTATION

Class	Drug examples	Most common	Other ILD patterns	Other pulmonary manifestations [0.2]
Disease-modifying antirheumatic drugs (DMARDs)				
Non-biologic DMARDS	Methotrexate	HP	NSIP, OP, DAD, EP	• Hilar lymphadenopathy • Pleural effusions
	Leflunomide	DAD	NSIP, OP, HP, EP	• Exacerbation preexisting ILD
Biologic DMARDs	TNF-alpha inhibitors: Infliximab, Etanercept, rarely Adalimumab	NSIP	OP, DAD, EP, granulomatous lung disease	• Activation of latent tuberculosis • Exacerbation preexisting ILD • SLE-like reactions, vasculitis
	Anti-CD20 MAb: Rituximab	OP	HP, DAD	• Severe COVID-19 pneumonitis (also reported with other anti-CD20 agents)
Tyrosine kinase inhibitors (TKIs)				
EGFR inhibitors	Erlotinib, Gefitinib, Osimertinib	OP	DAD, HP, NSIP; EP with Osimertinib	• Alveolar hemorrhage
ALK inhibitors	Crizotinib, Lorlatinib, Alectinib	DAD	NSIP, OP	
Bcr-Abl inhibitors	Imatinib, Dasatinib	PAH and effusions	Rare: EP, NSIP, OP	• Pulmonary arterial hypertension • Pleural effusions
Immune checkpoint inhibitors (ICIs)				
PD-1 inhibitors	Nivolumab, Pembrolizumab	OP	DAD, NSIP, HP, EP	• Sarcoid-like reaction in lung parenchyma and/ or thoracic lymph nodes • Alveolar hemorrhage • Cancer progression or pseudo-progression
PD-L1 inhibitors	Atezolizumab, Durvalumab	OP	DAD, HP, NSIP	
CTLA-4 inhibitor	Ipilimumab	OP	DAD	

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RADIOLOGICAL PATTERN AND OTHER PULMONARY MANIFESTATION

Class	Drug examples	Most common	Other ILD patterns	Other pulmonary manifestations [0.2]
Other anti-cancer therapies				
Cytotoxic chemotherapy	Bleomycin	OP	DAD, NSIP, EP, HP, advanced fibrosis	
	Busulfan	OP	NSIP, DAD, pulmonary alveolar proteinosis, AFOP	• Alveolar hemorrhage
	Cyclophosphamide	OP/NSIP	NSIP, OP, DAD, UIP	• PPFE in advanced stage • Alveolar hemorrhage
	Carmustine	DAD	NSIP, chronic fibrosis over decades	• Pneumothorax • PPFE in advanced stage
	Paclitaxel	OP/NSIP	DAD	• Acute bronchospasm
mTOR inhibitors	Sirolimus, Everolimus	OP	NSIP, HP, LIP	• Alveolar hemorrhage
Other agents				
Cardiac therapy	Amiodarone	Lipoid pneumonia	OP, DAD, AFOP, NSIP, chronic EP, chronic fibrosis	• Alveolar hemorrhage • Acute bronchospasm • SLE-like reaction • Pleural effusions • PPFE
Antibiotics	Nitrofurantoin	HP	OP, chronic EP, chronic pulmonary fibrosis	• Pleural effusions • Pulmonary vasculitis

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SYSTEMIC DRUG INDUCED SYNDROME

- DRESS syndrome (Drug rash with eosinophilia and systemic symptoms)

  -5- 25% patients may have lung involvement

  -Drugs: Minocycline and anticonvulsants

- Drug induced SLE :

  -Amiodarone, hydralazine, procainamide, methyldopa, isoniazid

- Pulmonary-renal syndrome:

  -Phenytoin, PTU, hydralazine, D-penicillamine

Distefano G, Fanzone L, Palermo M, et al. HRCT Patterns of Drug-Induced Interstitial Lung Diseases: A Review. Diagnostics. 2020

ROLE OF BRONCHOALVEOLAR LAVAGE

BAL

- Frequently non-diagnostic by itself
- BAL is usually done to rule out an infective cause
- Useful in diagnosing DAH (Pattern of drug- induced lung injury)
- any type of alveolitis (lymphocytic, neutrophilic, eosinophilic, or mixed)
- Amiodarone induced DILD shows foamy intracytoplasmic alterations and corresponds to a form of phospholipidosis - high specificity

U. Costabel et al Bronchoalveolar lavage in drug-induced lung disease Clin Chest Med 25 (2004) 25–35

BAL

Cellular analysis:

- Most common BAL cellular profile: Lymphocytosis (≥25% lymphocytes)
- Lymphocyte subset analysis (not recommended routinely)

a)CD8+ T cell predominance: Drug induced HP

b)CD_4+ T cell predominance: Methotrexate, sirolimus (Immunomodulatory drugs)

- ≥25% eosinophils: Acute or chronic eosinophilic pneumonia

U. Costabel et al Bronchoalveolar lavage in drug-induced lung disease Clin Chest Med 25 (2004) 25–35

ROLE OF LUNG BIOPSY

The role of transbronchial lung biopsy for the diagnosis of diffuse drug-induced lung disease: a case series of 44 patients

M. Romagnoli[1], C. Bigliazzi[1], G. Casoni[1], M. Chilosi[2], A. Carloni[3], A. Dubini[4], Ch. Gurioli[1], S. Tomassetti[1], C. Gurioli[1], V. Poletti[1]

[1] Interventional Pulmonology, Department of Thoracic Diseases, Forlì, Italy, [2] Institute of Pathology, University of Verona, Italy, [3] Institute of Radiology, Terni, Italy, [4] Institute of Pathology, Forlì, Italy

- Retrospective study
- Inclusion criteria- Suspected DILD who underwent bronchoscopy and biopsy
- Over a 5-yr period, 44 patients underwent bronchoscopy, and all had a bronchoalveolar lavage and 33 underwent TBLB.
- Thirty-three of the 44 patients underwent TBLB (75%), and the results of TBLB were diagnostically helpful in 25 (75.7%) of the procedures
- HP pattern- DAD (8),OP (8), HP(1), CIP (8)
- Conclusion : the clinical usefulness histology is arbitrary.

Prospective evaluation of drug-induced lung toxicity with high-resolution CT and transbronchial biopsy

- Prospective of 5 years duration, N= 42
- Compared the results of high resolution computed tomography (HRCT) and cyto histology after transbronchial biopsy in the evaluation of drug-related interstitial lung disease
- Transbronchial biopsy was performed in 38 patients
- HRCT patterns: noncardiogenic pulmonary oedema (n=13); organising pneumonia (OP) (n=9); hypersensitivity pneumonitis (HP) (n=2); alveolar haemorrhage (AH) (n=2); nonspecific interstitial pneumonia (NSIP) (n=5); lipoid pneumonia (LP) (n=1); sarcoid-like pattern (n=1).
- Cytohistological diagnosis DAD- 11 patients, OP in 7, HP in 3, AH in 3 , chronic interstitial pneumonia (CIP) in 8, LP in 3 and pseudosarcoidosis in 1.
- Sensitivity and specificity of the radiological analysis was good, which were 86% and 88% for OP and 100% and 93% for DAD.

Lung biopsy is not routinely recommended for patients suspected for DILD

HISTOLOGIC PATTERN IN ILD

Major histopathologic forms of ILD:

- Cellular and fibrotic NSIP
- Usual Interstitial pneumonia
- Hypersensitivity pneumonitis
- Organising pneumonia (with/without obliterative bronchiolitis)
- Eosinophilic pneumonia
- Desquamative interstitial pneumonias
- Diffuse alveolar damage

MANAGEMENT OF DI-ILD

Case Details

- 50 year old male
- Never smoker
- K/C/O DLBCL on R-CHOP

regimen since 2023

Last cycle- 13/5/2024

- SOB x 1months
- Cough x 2 weeks

Commonly used drugs

- Bleomycin
- Immune check point inhibitors
- Amiodarone
- DMARDS-Methotrexate

Challenges in management of DI-ILD

- **Lack of Evidence**: Treatments for drug-induced ILD are rarely evaluated in controlled clinical trials, leading to uncertainty in management strategies.
- **Unpredictable Prognosis**: Chemotherapy-induced ILD can result in severe or fatal outcomes, even with drug discontinuation and glucocorticoid therapy.
- **Guideline Limitations**: Current guidelines are based on observational reports and clinical experience, lacking standardization and validation through prospective trials.

BLEOMYCIN

BLEOMYCIN

Epidemiology :

- Incidence of bleomycin induced pneumonitis : 6% - 18%
- Overall mortality : 3% or less

Mechanism:

Free radical injury→ leak of endothelium → release of inflammatory cells like TNF alpha and TGF beta→ Fibroblast activation → Interstitial fibrosis

Hay J, Shahzeidi S, Laurent G. Mechanisms of bleomycin induced lung damage. Arch Toxicol. 1991

RISK FACTORS

- Age > 70 yrs /Higher cumulative dose (>400 units)
- Oxygen therapy (avoid O2 for 6 moths)
- Creatinine clearance < 35 ml/min
- Concurrent use with other chemotherapeutic agents(eg: ABVD regimen for Hodgkin Lymphoma)
- Radiation recall effect- avoid radiation for 28 days preceding bleomycin
- Smoking

Sleijfer S. Bleomycin-induced pneumonitis. Chest. 2001

BLEOMYCIN

Pulmonary Syndromes	Treatment	Comments
Chronic pneumonitis Pulmonary fibrosis Rare fulminant variant with acute respiratory failure	Discontinue drug Corticosteroids	Risk Factors: Cumulative dose >400 U, supplemental oxygen, therapeutic radiation, renal insufficiency, age >70 years, additional cytotoxic drugs
Hypersensitivity-type lung disease	Discontinue drug Corticosteroids	Dyspnea, cough, skin rash, and peripheral eosinophilia
Chest pain syndrome	Discontinue drug	Associated with drug infusion

Sleijfer S. Bleomycin-induced pneumonitis. Chest. 2001

Severe Bleomycin-Induced Pneumonitis*

Clinical Features and Response to Corticosteroids

Dorothy A. White, M.D., F.C.C.P.; and Diane E. Stover, M.D., F.C.C.P.

Sex, Age (yr)	Tumor	Units	Units/sq m	Roentgenogram	PO_2, mm Hg	Therapy	Response	Outcome
1, M, 67	Esophagus	180	100	Interstitial infiltrates right>left	65	None	. . .	Death, 3 days
2, M, 73	Esophagus	183	100	Bibasilar infiltrates	49	Prednisone (60 mg/day)	Clinical and radiographic improvement; no change in PFT	Death of cardiac cause, 6 wk
3, F, 44	Esophagus	248	132	Bilateral alveolar infiltrates	45	None	. . .	Death, 20 days
4, M, 49	Lymphoma	588	279	Bibasilar interstitial infiltrates	74	Methylpred-nisolone (60 mg/day)	Clinical and radiographic improvement; PFT, mild improvement; recurrence	Exertional dyspnea; late respiratory death, 15 mo
5, F, 62	Lymphoma	532	279	Interstitial infiltrates right>left; pneumo-mediastinum	77	Prednisone (100 mg/day)	Clinical improvement	Exertional dyspnea; death due to tumor, 9 mo
6, M, 44	Hodgkin's disease	?90	. . .	Normal	88	Prednisone (60 mg/day)	Clinical improvement; recurrence	Exertional dyspnea; off steroids, 20 mo
7, M, 58	Naso-pharynx	300	150	Bibasilar interstitial infiltrates	90	Prednisone (60 mg/day)	Clinical and radiographic improvement; no change in PFT	Asymptomatic; off steroids, 28 mo
8, M, 63	Pyriform sinus	180	90	Bibasilar interstitial infiltrates; pneumothorax	76	Prednisone (60 mg/day)	Clinical and radiographic improvement; no change in PFT; recurrence	Asymptomatic; late respiratory death, 12 mo
9, F, 61	Cervix	180	100	Alveolar infiltrate, right lung	76	Prednisone (100 mg/day)	Clinical improvement; recurrence	Exertional dyspnea; late respiratory death, 12 mo
10, F, 61	Cervix	136	82	Interstitial infiltrates, right lung	48	None	. . .	Death, 5 days

*PFT, Pulmonary function tests.

Dorothy A.et al Chest . 1984 Nov;86(5):723-8

Conclusion:

- Out of 286 patients, 10 developed pulmonary toxicity
- Case 1, 3,10 - diagnosis was unsuspected prior to death
- Case 8- Died due to BIP

Pulmonary toxicity following bleomycin use: A single-center experience

Article *in* Journal of Cancer Research and Therapeutics · July 2017

DOI: 10.4103/0973-1482.204887

- Retrospective analytic study from 1998 to 2012 (14 years)
- 22 patients who developed BIP after receiving bleomycin chemotherapy ,8 were Hodgkin's Disease (HD) and 14 were Germ Cell Tumor (GCT).
- Chemotherapy Regimens:

-ABVD (Adriamycin, Bleomycin, Vinblastine, Dacarbazine) for HD.

-BEP (Bleomycin, Etoposide, Cisplatin) for GCT.

- Intervention- Steroid 0.75-1 mg/kg 4-8 weeks which then gradually tapered over an additional 4-6 months, in accordance with clinical response.
- Baseline PFT- Normal

Madabhavi I. et al., Journal of Cancer Research and Therapeutics, 2017;13(3):466-470.

S.no	Age/Sex	Disease/Histology/Stage	Total Dose (units)	Predisposing Factors, Treatment, and Outcomes
1	65/Male	HD/MC/III	120	Older age, chest RT, chronic smoker (25 pack years). Symptomatic and given steroid in standard dose. Patient expired due to sepsis.
2	30/Male	HD/MC/III	160	Asymptomatic, no treatment required.
3	25/Female	HD/NS/III	160	Asymptomatic, no treatment required.
4	60/Male	HD/MC/II	120	Chest RT and older age were risk factors. Symptomatic and given steroid in standard dose.
5	30/Male	HD/NS/II	120	Chest RT was a risk factor. Symptomatic and given steroid in standard dose.
6	48/Male	HD/MC/III	160	Chronic smoker (20 pack years) was a risk factor. Symptomatic and given steroid in standard dose.
7	45/Male	HD/MC/III	160	Asymptomatic, no treatment required.

Madabhavi I. et al., Journal of Cancer Research and Therapeutics, 2017;13(3):466-470.

Serial Number	Age/Sex	Disease/Histology/Stage	Total Dose (units)	Predisposing Factors, Treatment, and Outcomes
8	55/Female	HD/NS/I	80	Chest RT was a risk factor. Asymptomatic, no treatment required.
9	22/Female	NGCT/IIB	360	Asymptomatic, no treatment required.
10	35/Male	NGCT/IIB	360	Symptomatic and given steroid in standard dose.
11	40/Male	NGCT/IIIC	360	Symptomatic and given steroid in standard dose.
12	41/Male	NGCT/IIB	360	Symptomatic and given steroid in standard dose.
13	35/Male	SGCT/IIIC (IR)	360	Symptomatic and given steroid in standard dose.
14	32/Male	NGCT/IIIC	360	Asymptomatic, no treatment required.

Madabhavi I. et al., Journal of Cancer Research and Therapeutics, 2017;13(3):466-470.

Steroid treatment

- 14 symptomatic patients were treated with Prednisone at a dose of 0.75-1 mg/kg for 4-8 weeks, with gradual tapering over an additional 4-6 months based on clinical response.
- Close monitoring of side effects during steroid therapy was conducted.
- Noninvasive ventilation: Required by 4 patients, along with oxygen therapy, nebulization (steroids, beta agonists), and antibiotics.
- Mechanical ventilation: Required by 2 patients (both later died of multiorgan failure).

S.no	Age/Sex	Disease/Histology/Stage	Total Dose (units)	Predisposing Factors, Treatment, and Outcomes
15	24/Male	SGCT/IIIB (GR)	270	Symptomatic and given steroid in standard dose.
16	24/Male	SGCT/IIB (IR)	360	Asymptomatic, no treatment required.
17	28/Male	SGCT/IIIB	360	Symptomatic and given steroid in standard dose.
18	32/Male	NGCT/IIIC	360	Symptomatic and given steroid in standard dose. Patient expired due to ARDS.
19	33/Male	NGCT/IIB	360	Symptomatic and given steroid in standard dose.
20	40/Female	SGCT/IIIC (IR)	360	Symptomatic and given steroid in standard dose.
21	20/Male	NGCT/IIIB	360	Symptomatic and given steroid in standard dose.
22	22/Male	NGCT/IIIB	360	Symptomatic and given steroid in standard dose.

Madabhavi I. et al., Journal of Cancer Research and Therapeutics, 2017;13(3):466-470.

Beyond Conventional Therapy: Role of Pulse Steroids in Bleomycin Induced Lung Injury

Raghav Gupta MD and Neil A Ettinger MD

- 65-year-old female diagnosed with Stage IV Hodgkin lymphoma.
- Treated with 4 cycles of ABVD chemotherapy (including 126 units of bleomycin).
- Presented with progressive dyspnea, SpO_2 of 88% on room air.
- HRCT showed bilateral interstitial infiltrates, fibrosis, and patchy ground-glass opacities.
- Diagnosis: clinical symptoms, HRCT findings, and severe restrictive lung defect (FVC: 21% of predicted).Fiber optic bronchoscopy and biopsy revealed acute lung injury, type II pneumocyte hyperplasia, and organizing pneumonia.

Gupta, R., & Ettinger, N. A. (2013). Beyond Conventional Therapy: Role of Pulse Steroids in Bleomycin Induced Lung Injury. Respiratory Care, 59(1),

Treatment

- Initially started on low-dose IV methylprednisolone (60 mg every 8 hours) and N-acetylcysteine.
- Conventional therapy failed: Pulse Steroid Therapy: High-dose methylprednisolone (1 g IV daily) was initiated after 1 week.
- Rapid clinical improvement within 1-2 days: Oxygen requirement reduced from 30 L/min to 6 L/min.
- Patient was discharged on a prednisone tapered over 8 weeks.

Gupta, R., & Ettinger, N. A. (2013). Beyond Conventional Therapy: Role of Pulse Steroids in Bleomycin Induced Lung Injury. Respiratory Care, 59(1),

Role of Imatinib in BIP?

- The interest in imatinib stems from their antifibrotic property.
- Mechanism of action :

- Specific tyrosine kinase inhibitor of BCR-ABL, PDGFR.
- Suppresses the transformation of fibroblasts into myofibroblasts and reduces collagen deposition by inhibiting PDGFR and TGF-β signaling involved in pathogenesis of BIP

Aykac , Tecimer.,Turk Thorac J 2020; 21(6): 457-60

REFERENCES	DISEASE	PRESENTATION	INTERVENTION	OUTCOME	FOLLOWUP
Carnevale et al 2011	Stage 4 Hodgkin Lymphoma (HL) Dose- Bleomycin 10U/m2	• Respiratory failure requiring NIV • HRCT- Bilateral GGO with reticulations and honeycombing	1) Methylprednisolone 2mg/kg/d 2) Imatinib 300mg/d	Improved after 3weeks	IM- 6 months HRCT Scan – 3 and 6 months Alive, complete remission for HL
Aykac et al 2020	Seminona Bleomycin, Etopsoside Cisplatin	• RF requiring NIV • HRCT- Bilateral consolidation • Biopsy- fibroblastic proliferation	1) Methylprednisolone 0.75 mg/kg/day 2) Prednisolone 100mg 3) Imatinib 300mg	Improved after 1 week, Complete resolution – 4 months	IM- 9 months Steroids- 5 month Alive -3years

Carnevale-Schianca F, et al. Journal of Clinical Oncology, 2011;29(24):e691-3
Aykac , Tecimer.,Turk Thorac J 2020; 21(6): 457-60

Pirfenidone as salvage treatment for refractory bleomycin-induced lung injury: a case report of seminoma

Koji Sakamoto*†, Satoru Ito*†, Naozumi Hashimoto and Yoshinori Hasegawa

- 3-year-old male with recurrent seminoma, treated with cisplatin, etoposide, and bleomycin (PEB regimen).
- Developed dry cough, fever, and bilateral lung infiltrates on HRCT after the second chemotherapy cycle.
- Diagnosis: Bleomycin-induced lung injury (BILI).
- Started on oral prednisolone (30 mg/day), which initially improved symptoms and radiologic findings.

Sakamoto, K., et al. (2017). Pirfenidone as salvage treatment for refractory bleomycin-induced lung injury: a case report of seminoma.

Table 1 Pulmonary function tests and serum markers

	Before corticosteroid pulse therapy	2 months post corticosteroid pulse therapy	8 months post corticosteroid pulse therapy, before pirfenidone	1 year after starting pirfenidone therapy
Pulmonary Function				
VC (L)	2.60	3.62	3.75	4.12
%VC	78.6	102.4	106.4	103.1
TLC (L)	4.52	5.71	5.53	6.65
%TLC	77.4	97.8	94.5	106.3
DLco(mL/min/mmHg)	11.24	14.70	14.71	15.89
%DLco	56.5	72.8	72.6	78.9
Serum Marker				
KL-6 (U/mL)	472	412	326	287
LDH (IU/L)	328	307	319	237

Sakamoto, K., et al. (2017). Pirfenidone as salvage treatment for refractory bleomycin-induced lung injury: a case report of seminoma.

Course

- Treated with four courses of methylprednisolone (1 g/day) for 3 days, resulting in significant symptom relief and radiologic improvement.
- Maintenance therapy with oral prednisolone (15 mg/day).
- Recurrence: After chemotherapy, exertional dyspnea and new opacities appeared on HRCT despite maintenance corticosteroid therapy.

Sakamoto, K., et al. (2017). Pirfenidone as salvage treatment for refractory bleomycin-induced lung injury: a case report of seminoma.

Outcome

- Pirfenidone (1800 mg/day) added due to worsening lung opacities on HRCT and corticosteroid complications.
- Outcome: Marked improvement in lung function, with regression of ground-glass and reticulonodular opacities after 3 months of pirfenidone therapy.
- Final Outcome: Steroid dose tapered to 2 mg/day, with continued improvement in lung function.
- 1-year follow-up: No recurrence of lung injury, with stable pulmonary function on low-dose steroids and pirfenidone.

Sakamoto, K., et al. (2017). Pirfenidone as salvage treatment for refractory bleomycin-induced lung injury: a case report of seminoma.

Recommendations

- Prevention: Baseline PFTs (including DLCO) are essential before starting bleomycin.
- Avoid cumulative bleomycin doses exceeding 400 units.
- Maintain a 4-week interval between chemotherapy and chest radiotherapy to reduce risk.
- Surveillance: Regular imaging monitoring at 6-month intervals for early detection of BIP.

AMIODARONE

AMIODARONE

- Widely used antiarrhythmic
- Lipid soluble - deposited in adipose tissue, thyroid, lungs and liver
- Half life : 30 – 100 days
- Presentation :

a) Acute - occur as early as 2 days to 2 weeks

b) Chronic- months to years

Feduska ET, Thoma BN, Torjman MC, Goldhammer JE. Acute amiodarone pulmonary toxicity. J Cardiothorac Vasc Anesth. 2021

RISK FACTORS:

- Older age
- Duration of therapy >2 months
- Occurs in 10% of patients who used medication for 1 year
- Dose dependent: > 400 mg/day for 2 months
- Male
- Renal disease
- Pre-existing lung disease

Feduska ET, Thoma BN, Torjman MC, Goldhammer JE. Acute amiodarone pulmonary toxicity. J Cardiothorac Vasc Anesth. 2021

AMIODARONE

ACUTE

- Pneumonitis
- Pulmonary alveolar hemorrhage
- ARDS

Mechanism:

- Idiosyncratic
- production of unstable aryl radicals – ROS production
- Direct cellular injury - Apoptosis

CHRONIC

- CEP
- OP
- Pulmonary fibrosis

Mechanism:

- Impair normal phospholipid catabolism in lysosomes -> cellular phospholipidosis -> cell injury

Feduska ET, Thoma BN, Torjman MC, Goldhammer JE. Acute amiodarone pulmonary toxicity. J Cardiothorac Vasc Anesth. 2021

MANAGEMENT

- Radiology:

a)Typical pattern: diffuse or patchy interstitial or mixed alveolar-interstitial infiltrates which can be either unilateral or bilateral (Honeycombing is rare)

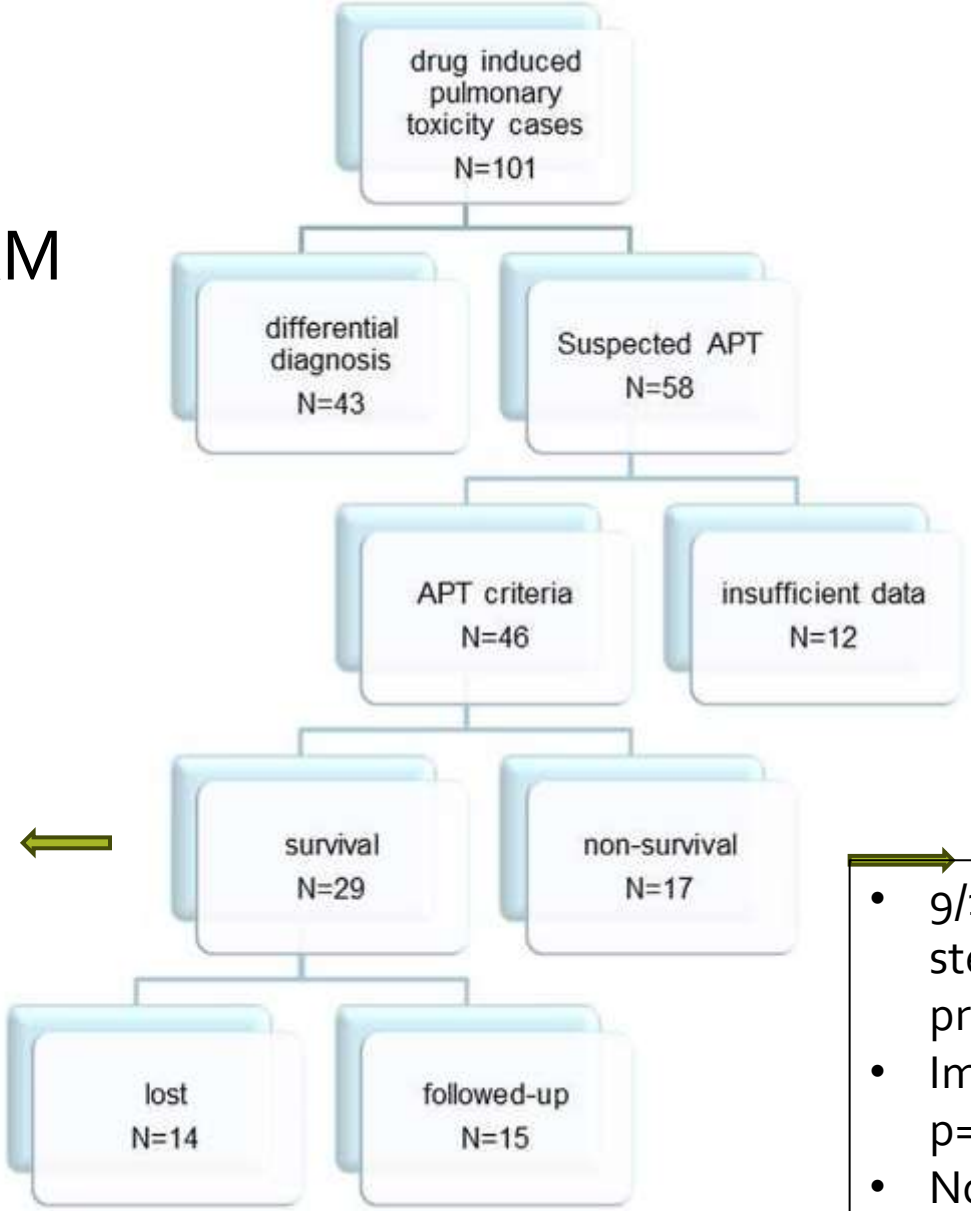
b)Should be considered in cases of migratory infiltrates that are consistent with OP but poorly responsive to steroids

- BAL : Lymphocytosis (CD8), abundant alveolar macrophages with “foamy” cytoplasm

Feduska ET, Thoma BN, Torjman MC, Goldhammer JE. Acute amiodarone pulmonary toxicity. J Cardiothorac Vasc Anesth. 2021

Mankikian et.al.,2014	**Initial characteristics and outcome of hospitalized patients with amiodarone pulmonary toxicity**
STUDY DESIGN	Retrospective cohort between 2000-2011
OBJECTIVE	factors associated with mortality and to describe outcome and sequelae of patients with APT.
PARTICIPANTS	101 cases reviewed, 46 diagnosed as APT
INCLUSION AND EXCLUSION CRITERIA	• Patients on amiodarone therapy with new or worsening respiratory symptoms. • Presence of new pulmonary infiltrates on HRCT or chest X-ray • Exclusion of other diagnoses (e.g., cardiogenic edema, sepsis).
METHODOLOGY	2 groups based on survival at day 90. The evolution of 15 survivors was evaluated at 3 months and 12 months post-diagnosis

CONSORT DIAGRAM



- Corticosteroid [0.5-5 mg/kg]- 22 (76%)
- ICU admission – 16(55%)
- Mechanical ventilation – 11(38%)

- Corticosteroid treatment- 16(94%)
- ICU admission - 9(53%)
- Mechanical ventilation - 8(47%)

- 9/15 (60%) received steroids (more severe presentation)
- Improvement in MMRC (p=0.007) and VC (p=0.02)
- No difference in HRCT evolution

HRCT characteristics of surviving and non-surviving patients with amiodarone pulmonary toxicity. Ground-glass opacities and alveolar consolidations were quantified to give an active lesion score (or HRCT alveolar score), while traction bronchiectasis, scissural distortions and honeycombing were considered to represent fibrotic lesions and were quantified to produce an HRCT fibrosis score. Six areas of the lung were defined: the upper, middle and lower zones. Opacity intensity on thin section HRCT was scored semi-quantitatively: 1 = less than 25% of total lung parenchyma in the area, 2 = 25–50%, 3 = 50–75%, 4 = more than 75%, yielding a total score (total: 0–24). The other HRCT abnormalities were noted if present. All quantitative data are expressed as median [range] values.

HRCT score	Survival (n = 22)	Non-survival (n = 13)	P
Alveolar score (/24)			
upper areas	5 [2; 8]	7 [4; 8]	0.006
middle areas	6 [2; 7]	7 [6; 8]	0.008
inferior areas	6 [2; 8]	6 [4; 8]	0.972
Total	18 [8; 23]	20 [17; 23]	0.004
upper/lower gradient	−1 [−5; 4]	1 [−3; 5]	0.061
Total fibrosis score (/24)	2 [0; 5]	0 [0; 4]	0.149
Adenopathy, n (%)	13 (59%)	6 (46%)	0.458
Pleural effusion, n (%)	5 (23%)	7 (54%)	0.079
Interlobular septa thickening, n (%)	15 (68%)	10 (77%)	0.709
Intralobular reticulation, n (%)	20 (91%)	10 (77%)	0.337
Crazy paving, n (%)	16 (73%)	10 (77%)	0.680
Lobular attenuation, n (%)	15 (68%)	9 (69%)	0.630

- 1. The HRCT alveolar score decreased by over 40% at medium term.
- 2. Fibrotic lesions increased significantly, observed in 10 out of 15 patients

Consensus statement for the diagnosis and treatment of drug-induced lung injuries ☆

Keishi Kubo[a,], Arata Azuma[b], Minoru Kanazawa[c], Hideto Kameda[d], Masahiko Kusumoto[e], Akihiko Genma[b], Yasuo Saijo[f], Fumikazu Sakai[g], Yukihiko Sugiyama[h], Koichiro Tatsumi[i], Makoto Dohi[j], Hitoshi Tokuda[k], Shu Hashimoto[l], Noboru Hattori[m], Masayuki Hanaoka[a], Yuh Fukuda[n], the Japanese Respiratory Society Committee for formulation of Consensus statement for the diagnosis and treatment of drug-induced lung injuries*

- Discontinuation of Amiodarone: May be sufficient if disease extent is limited.
- Corticosteroid Therapy: Patients with substantial involvement on imaging or hypoxemia.

Evidence for Corticosteroid Use:

- Clinical Evidence: Accumulated support for beneficial effects despite lack of controlled studies.
- Considerations: Initial dosage (e.g., 0.75–1.0 mg/kg prednisolone).

Goldschlager, N. et al. (2007). A Practical Guide for Clinicians Who Treat Patients with Amiodarone: 2007. Heart Rhythm, 4(9), 1250-1259

Consensus statement

- Corticosteroid Tapering: Slow reduction of corticosteroid over more than 6 months, Maintenance: Until clinical response
- Monitoring: Careful monitoring after discontinuation of corticosteroids.
- Imaging and Pulmonary Function: Improvement generally lags behind clinical improvement.
- If no improvement is detected after 1–2 months of corticosteroids, consider diagnoses other than amiodarone-induced pulmonary toxicities.

Goldschlager, N. et al. (2007). A Practical Guide for Clinicians Who Treat Patients with Amiodarone: 2007. Heart Rhythm, 4(9), 1250-1259

When to Consult a Pulmonologist?

1. Abnormal chest radiography at baseline or follow-up evaluation.
2. Abnormal FVC and DLCO at baseline or follow-up evaluation.
3. New cough and/or dyspnea (unexplained)

What we should do ?

For suspected amiodarone toxicity

- PFT- spirometry and DLCO
- HRCT chest

Goldschlager, N. et al. (2007). A Practical Guide for Clinicians Who Treat Patients with Amiodarone: 2007. Heart Rhythm, 4(9), 1250-1259

METHOTREXATE

METHOTREXATE

- Non-biologic DMARD
- Dihydrofolate reductase inhibitor
- seen even in low doses (7.5mg/week) and increased risk with higher doses
- Presentation- within 2 years , also as early as 1 month
- Incidence: Varies between 0.86% and 6.9%, most commonly occurring within the first year of treatment.

Sakamoto, K., et al. (2017). Pirfenidone as salvage treatment for refractory bleomycin-induced lung injury: a case report of seminoma.

Methotrexate pneumonitis: review of the literature and histopathological findings in nine patients

S. Imokawa, T.V. Colby, K.O. Leslie, R.A. Helmers

- The study evaluated 123 cases of MTX-induced pneumonitis.
- Symptomatic patients (101): Most developed cough, dyspnea, fever, and tachypnea (acute/subacute presentation- most).
- Asymptomatic patients: diagnosed by routine imaging.
- Steroids supplement: moderate to severe pneumonitis, particularly those with hypoxia or severe respiratory symptoms. (39 Patients received prednisolone 5-50 mg/day, or MPS 4 mg/day)

Imokawa, S., Colby, T. V., Leslie, K. O., & Helmers, R. A. (2000). Methotrexate pneumonitis: review of the literature and histopathological findings in nine patients. European Respiratory Journal, 15(2), 373-381.

Table 6. – Summary of therapeutic and follow-up data of methotrexate (MTX) pneumonitis literature review

	Total	Histological study (n=49)
Therapy		
Discontinuation of MTX	32	11
Discontinuation of MTX+steroid	65	30
Other therapies/not fully described	26	8
Continuation of MTX	8	2
Reintroduction of MTX	16	6
Recurrence	4	4
No recurrence	12	2
Follow-up (n=121)		
Improving	99	31
Progressive disease	1	0
Death caused by respiratory disease	16	14

Follow up :

- 99 improved, some of whom resolved completely

.

- There were 21 (15.8%) deaths ,16 caused by respiratory disease

- Methotrexate was continued in eight cases and all improved without steroid therapy.

- Sixteen additional patients were treated with reintroduction of MTX ,resulting in recurrence of pneumonitis in 25%

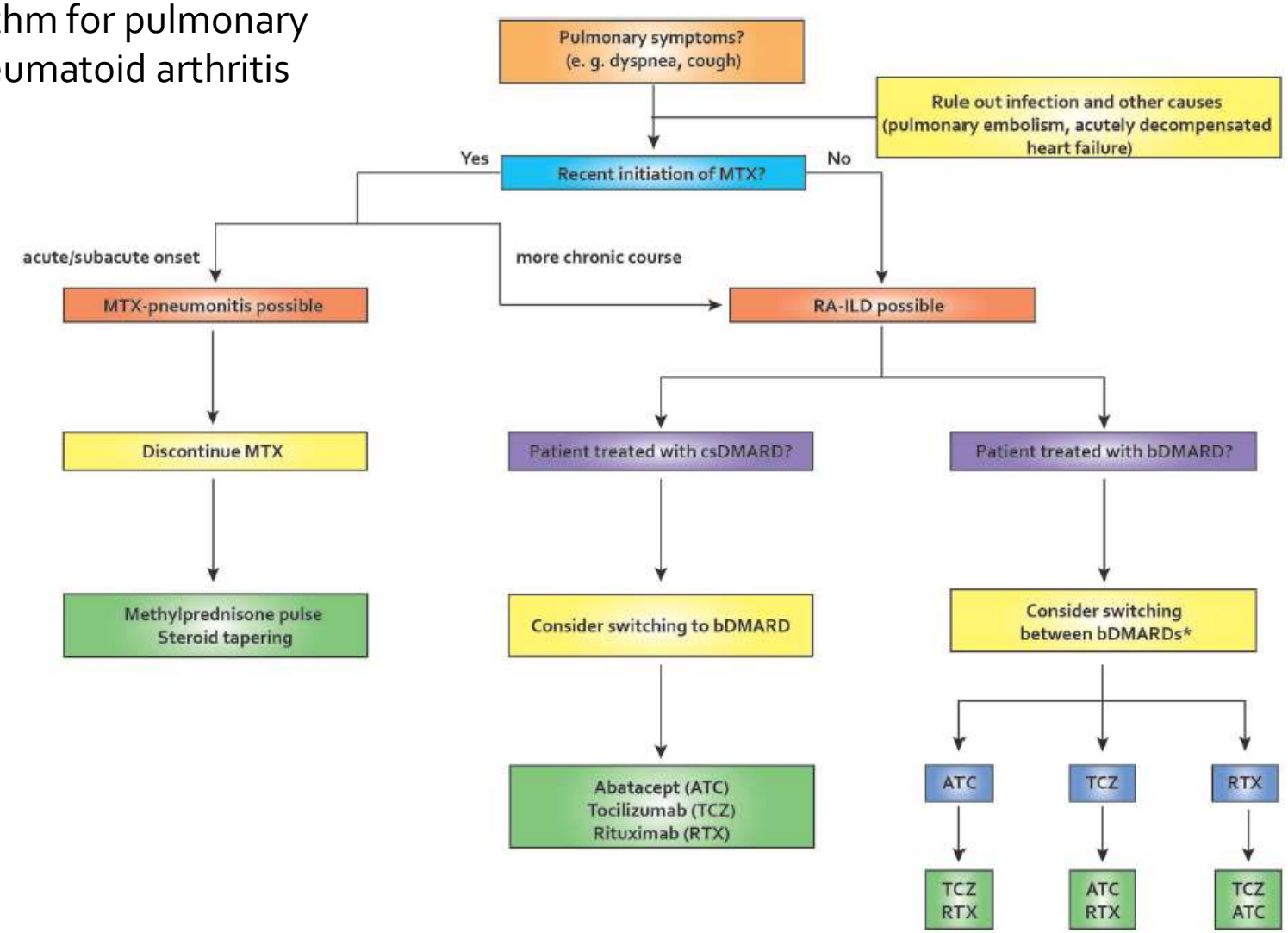
Imokawa, S., Colby, T. V., Leslie, K. O., & Helmers, R. A. (2000). Methotrexate pneumonitis: review of the literature and histopathological findings in nine patients. European Respiratory Journal, 15(2), 373-381.

Table 7. – Clinical features of methotrexate (MTX) pneumonitis: current study

Pt No.	Age yrs	Sex	Background disease	MTX dose	Therapy duration	Duration of respiratory symptoms	Symptoms	Phys exam	Chest XR findings	Path findings	Outcome/ Follow-up duration
1	71	F	RA	7.5	3 months	2–3 weeks	Dyspnoea, chest pain	Cr; TPN	Interstitial+ nodular, diffuse, lower lobe-dominant	CII+Gr	Alive, improved completely 1 week
2	74	F	RA	20	16 weeks	1–2 months	Dyspnoea, cough, sputum, fever	Cr; TPN	Hyperinflation	CII+Gr	Alive, improving 6 weeks
3	71	M	RA	NA	5 months	2 weeks	Dyspnoea, dry cough	Cr; TPN	Interstitial diffuse	DAD	Dead 9 days
4	65	M	RA	7.5	4 yrs	1 month	Dyspnoea; fever		Interstitial, bilateral	DAD	Dead 6 days
5	76	M	RA	7.5	11 months	1 month	Dyspnoea, dry cough	Cr	Interstitial bilateral	CII	Alive, improving 6 weeks
6	57	F	Psoriasis	2.5	6 months	1–2 weeks	Dyspnoea, dry cough, fever	Cr	Interstitial lower lobe-dominant	CII+ Gr	Alive, improving 3 weeks
7	64	F	Psoriasis	15	3 months	10 days	Dyspnoea, dry cough		Infiltrate, bilateral, lower lobe-dominant	DAD	Alive, improved but chronic respiratory failure 19 months
8	70	F	Polymyalgia rheumatica	15	3.5 months	Several days	Dyspnoea, dry cough, fever	Cr	Interstitial+ alveolar, bilateral, lower lobe-dominant	DAD	Alive, improving 3 weeks
9	74	F	RA/giant cell arteritis	15	36 months	Several weeks	Dyspnoea, dry cough, chest pain	Cr	Interstitial+ alveolar lower lobe-dominant	CII	Alive, improving 5 months

Imokawa, S., Colby, T. V., Leslie, K. O., & Helmers, R. A. (2000). Methotrexate pneumonitis: review of the literature and histopathological findings in nine patients. European Respiratory Journal, 15(2), 373-381.

Proposed algorithm for pulmonary symptoms in rheumatoid arthritis



Fragoulis, G. E., et al. (2019). Methotrexate-Associated Pneumonitis and Rheumatoid Arthritis-Interstitial Lung Disease: Current Concepts for the Diagnosis and Treatment. *Frontiers in Medicine, 6*, 238.

Risk factors and intervention

a)Pre-existing lung disease: Meta-analysis of six studies shows a 7.5-fold increased risk.

b)old age

c) previous DMARD

Screening Before MTX:

a) Baseline chest radiograph (CXR) and pulmonary function tests (PFTs) including FEV1, VC, and TLCO.

b) If TLCO < 70%, perform HRCT to detect interstitial lung disease (ILD).Avoid MTX in patients with significant ILD.

SEARLES AND McKENDRY DIAGNOSTIC CRITERIA

MAJOR CRITERIA

- Hypersensitivity pneumonitis by histopathologic examination
- Radiologic evidence of pulmonary interstitial or alveolar infiltrates
- Blood and sputum cultures negative for pathogenic organisms

MINOR CRITERIA

- Shortness of breath of <8 weeks duration
- Nonproductive cough
- O_2 saturation ≤90% on room air
- DLCO ≤70% predicted
- WBC ≤15,000/mm^3

Definite: Major criterion 1, or major criteria 2 and 3, and at least 3 minor criteria

Probable: Major criteria 2 and 3, and 2 minor criteria

Searles G, McKendry RJ. Methotrexate pneumonitis in rheumatoid arthritis: potential risk factors. Four case reports and a review of the literature. J Rheumatol. 1987

Recommendations

Baseline Testing:

- Baseline testing: CXR, PFTs (including TLCO).
- Avoid MTX in patients with reduced TLCO (<70%) or significant ILD.
- Consider HRCT if TLCO is <70% to rule out interstitial lung disease.
- Alternative DMARDs (e.g., azathioprine, cyclophosphamide) should be considered in patients with ILD or those at high risk.

Fragoulis GE, Nikiphorou E, Larsen J, et al. Methotrexate associated pneumonitis and rheumatoid arthritis-interstitial lung disease: current concepts for the diagnosis and treatment. Front Med (Lausanne). 2019

METHOTREXATE

PULMONARY SYNDROMES	TREATMENT	COMMENTS
▪ Chronic pneumonitis ▪ Pulmonary fibrosis	▪ Corticosteroids ▪ Discontinue drug	▪ Mc syndrome ▪ Risk Factors: Older age, Diabetes, previous use of dmrads, hypalbuminemia
▪ Hypersensitivity-type lung disease	▪ Discontinue drug ▪ Corticosteroids	▪ May resolve even if drug is continued, but can progress to fibrosis
▪ Chest pain syndrome	▪ Discontinue drug	▪ Associated by pleural effusions
▪ Non cardiogenic pulmonary edema	▪ Supportive care ▪ Discontinue drug	▪ Associated with intrathecal administration

Alarcon GS, Kremer JM, Macaluso M, et al. Risk factors for methotrexate-induced lung injury in patients with rheumatoid arthritis. A multicenter, case-control study. Methotrexate-Lung Study Group. Ann Intern Med. 1997

IMMUNE CHECKPOINT INHIBITORS

CHECKPOINT INHIBITOR IMMUNOTHERAPY

DRUG	PULMONARY SYNDROME	TREATMENT	COMMENTS
PD-1- Pembrolizumab , Nivolumab PDL1 - Atezolizumab , Durvalumab and Avelumab CTLA4 inhibitors – Ipilimumab	Pneumonitis	Discontinue drug	Rechallenge based on severity
	Organising pneumonia	Corticosteroids	May persist or recur despite drug discontinuation
	Sarcoid like toxicity	Secondary to immunosuppression for steroid refractory toxicity	RF: combination of anti-PDL1 / antiCTLA4 therapy , preexisting ild . Prior thoracic RT, EGFR combination Squamous NSCLSC histology

Johkoh T,et al. Chest CT diagnosis and management of drug-related pneumonitis: Fleischner Society position paper. Chest, 2021;159

Pneumonitis in Patients Treated With Anti–Programmed Death-1/Programmed Death Ligand 1 Therapy

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- Study Population: 915 patients across two institutions(578 patients from MSKCC, 337 from MIA)
- Patients treated with anti–PD-1/PD-L1 monotherapy or combination with anti–CTLA-4 monoclonal antibodies (mAbs).
- 441 monotherapy patients, 137 combination therapy patients.

Naidoo, J., et al. (2016). Pneumonitis in Patients Treated With Anti–Programmed Death-1/Programmed Death Ligand 1 Therapy. Journal of Clinical Oncology, 35(7), 709-717

Outcome

- Incidence: 43 cases (5%) developed pneumonitis.
- More common in combination therapy (10%) than monotherapy (3%).
- Treatment response:88% improved or resolved with drug holding and/or immunosuppression.
- 5 patients worsened and died due to pneumonitis or related infections.
- Rechallenge: 12 patients restarted immunotherapy, with 25% developing recurrent pneumonitis.

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Pneumonitis With Anti–PD-1/PD-L1 Therapy

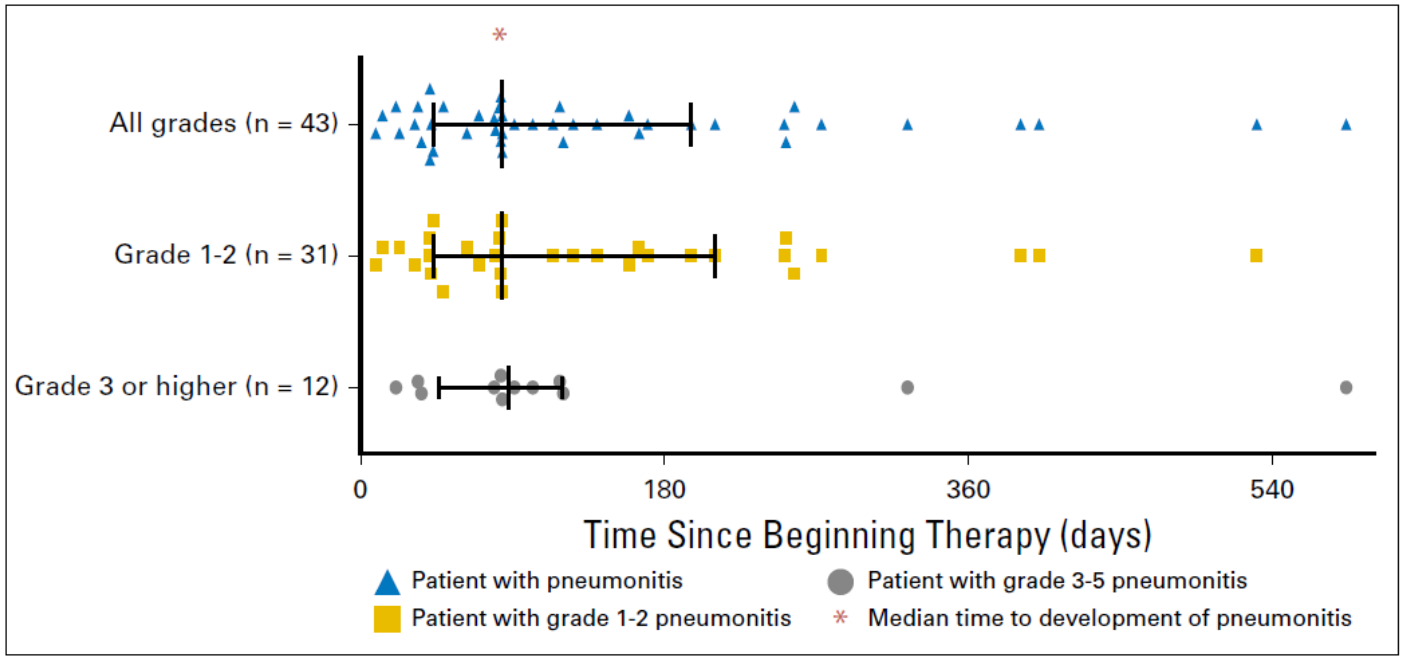

Fig 1. Time from first dose of anti–programmed death-1/programmed death ligand 1 therapy to date of pneumonitis event stratified by grade, with interquartile range and median values shown.

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Grades of severity

- Grade 1–2 pneumonitis: Managed mostly as outpatients (81%), with only 19% (all grade 2) hospitalized.
- Grade 3 or higher pneumonitis: All required hospitalization, starting with oral/IV corticosteroids, with 42% needing additional immunosuppression (e.g., infliximab, cyclophosphamide).
- Grade 1 pneumonitis: Majority treated by holding the drug (88%), with 12% requiring oral corticosteroids.
- Corticosteroid treatment: Of those treated (65%, 28 of 43), 61% began with oral, and 39% with IV corticosteroids.
- Median corticosteroid use: Starting dose of 50 mg prednisone (range 20–80 mg), with a median duration of 68 days (range 20–154 days).

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Table 3. Pneumonitis Management and Outcomes

	Highest Treatment Required for Pneumonitis Management, No. (%)				
Highest CTCAE Grade	Treatment Hold	Oral Corticosteroids	Intravenous Corticosteroids	Additional Immunosuppression*	Total
1	15 (83)	2 (12)	0 (0)	0 (0)	17
2	0 (0)	10 (71)	4 (29)	0 (0)	14
3	0 (0)	2 (20)	4 (40)	4 (40)	10
4	0 (0)	0 (0)	1 (100)	0 (0)	1
5	0 (0)	0 (0)	0 (0)	1 (100)	1
Total	15	14	9	5	43

	Clinical Outcomes of Pneumonitis Management, No. (%)				
	Completely Resolved	Improved	Worsened	Unknown	Total
1	17 (100)	0 (0)	0 (0)	0 (0)	17
2	10 (71)	3 (21)	0 (0)	1 (8)	14
3	4 (40)	2 (20)	4 (40)	0 (0)	10
4	1 (100)	0 (0)	0 (0)	0 (0)	1
5	0 (0)	0 (0)	1 (100)	0 (0)	1
Total	32	5	5	1	43

Abbreviation: CTCAE, Common Terminology Criteria for Adverse Events (version 4).
*Additional immunosuppression: Three patients received infliximab alone (all grade 3), and two patients received both infliximab and cyclophosphamide (one grade 3 and one grade 5).

Naidoo, J., et al. (2016). Pneumonitis in Patients Treated With Anti–Programmed Death-1/Programmed Death Ligand 1 Therapy. Journal of Clinical Oncology, 35(7), 709-717

Role of Infliximab in Immune Checkpoint Inhibitor-Induced Pneumonitis

Kathryn A. Lai,[1] Ajay Sheshadri,[2] Andres M. Adrianza,[2] Mikel Etchegaray,[3] Diwakar D. Balachandran,[2] Lara Bashoura,[2] Vickie R. Shannon,[2] Saadia A. Faiz[2]

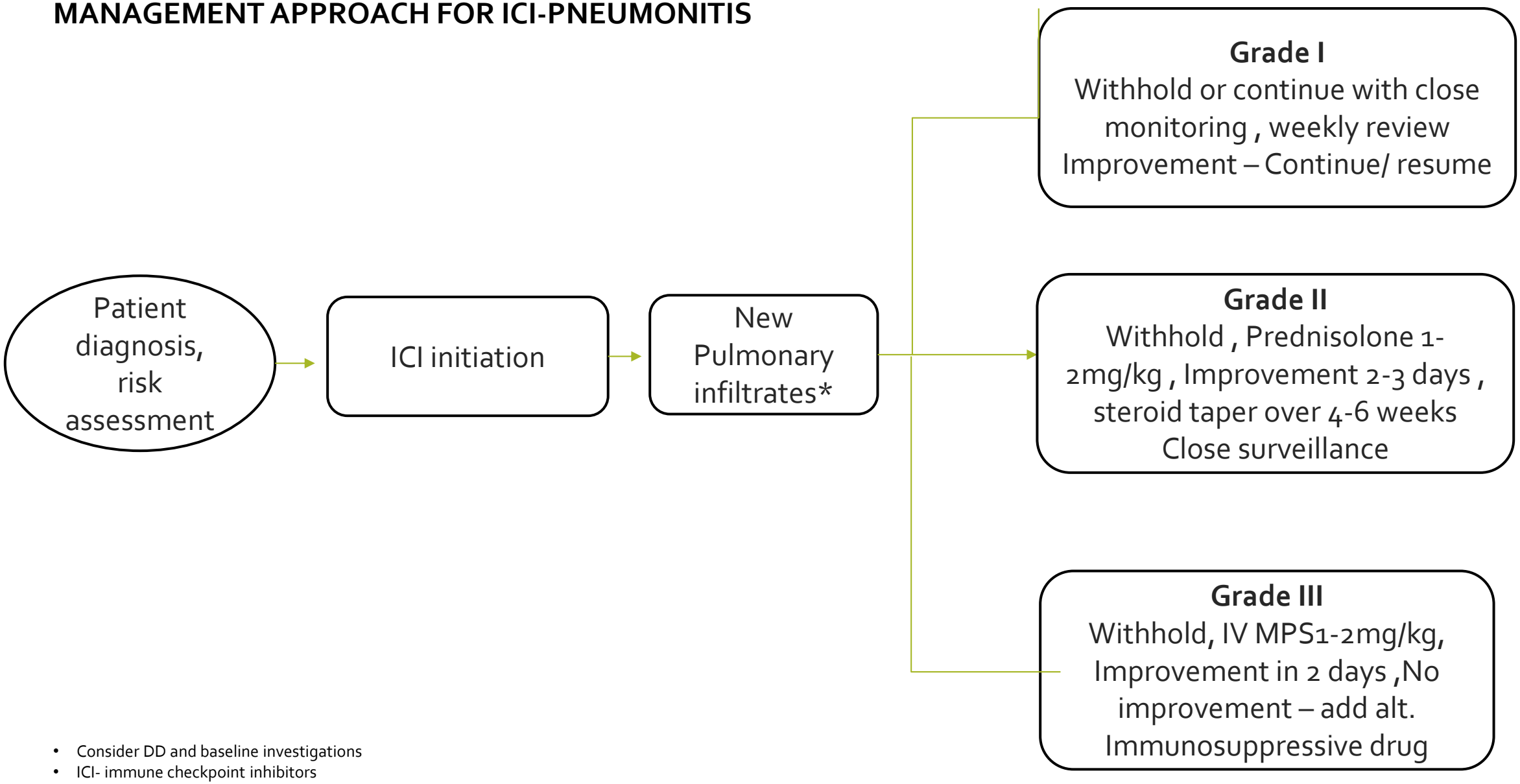
Table 1.—Patient characteristics receiving infliximab for grade 3 and 4 pneumonitis

Case	Age, Years	Sex	Cancer	Immunotherapy	Corticosteroid, mg/kg*	Time, Days^	Ventilatory Support, FiO2%	irAEs	Bronchoscopy, Lymphocytes, %	Outcome
1	66	M	Melanoma	Ipilimumab	1.2	2	Nasal cannula, 24%	–	No	Improved
2	66	M	Pancreatic	Ipilimumab	1.3	5	High-flow, 45%	Hepatic[&]	No	Improved
3	52	F	AML	Ipilimumab, nivolumab	3.3	9	High-flow, 60%	–	Yes[‡]	Improved
4	69	F	AML	Ipilimumab, nivolumab	1.1	7	MV, 90%	Dermatologic, gastrointestinal	Yes[‡]	Improved
5	79	M	AML	Nivolumab	2.4	34	High-flow, 50%	Renal	Yes, 13	Death[+]
6	72	M	AML	Ipilimumab, nivolumab	1.1	Chronic	High-flow, 30%	Hematologic	Yes, 26	Death[+]
7	72	F	MDS	Ipilimumab, nivolumab	2.0	2	BiPAP, 70%	Dermatologic	Yes, 18	Death
8	68	F	Lung	Nivolumab	0.8	9	High-flow, 75%	–	No	Death
9	61	M	Urothelial	Nivolumab	1.2	7	High-flow, 75%	–	Yes[‡]	Death

Lai, K. A., et al. (2020). Role of Infliximab in Immune Checkpoint Inhibitor-Induced Pneumonitis. Journal of Immunotherapy and Precision Oncology, 3(4), 172-174

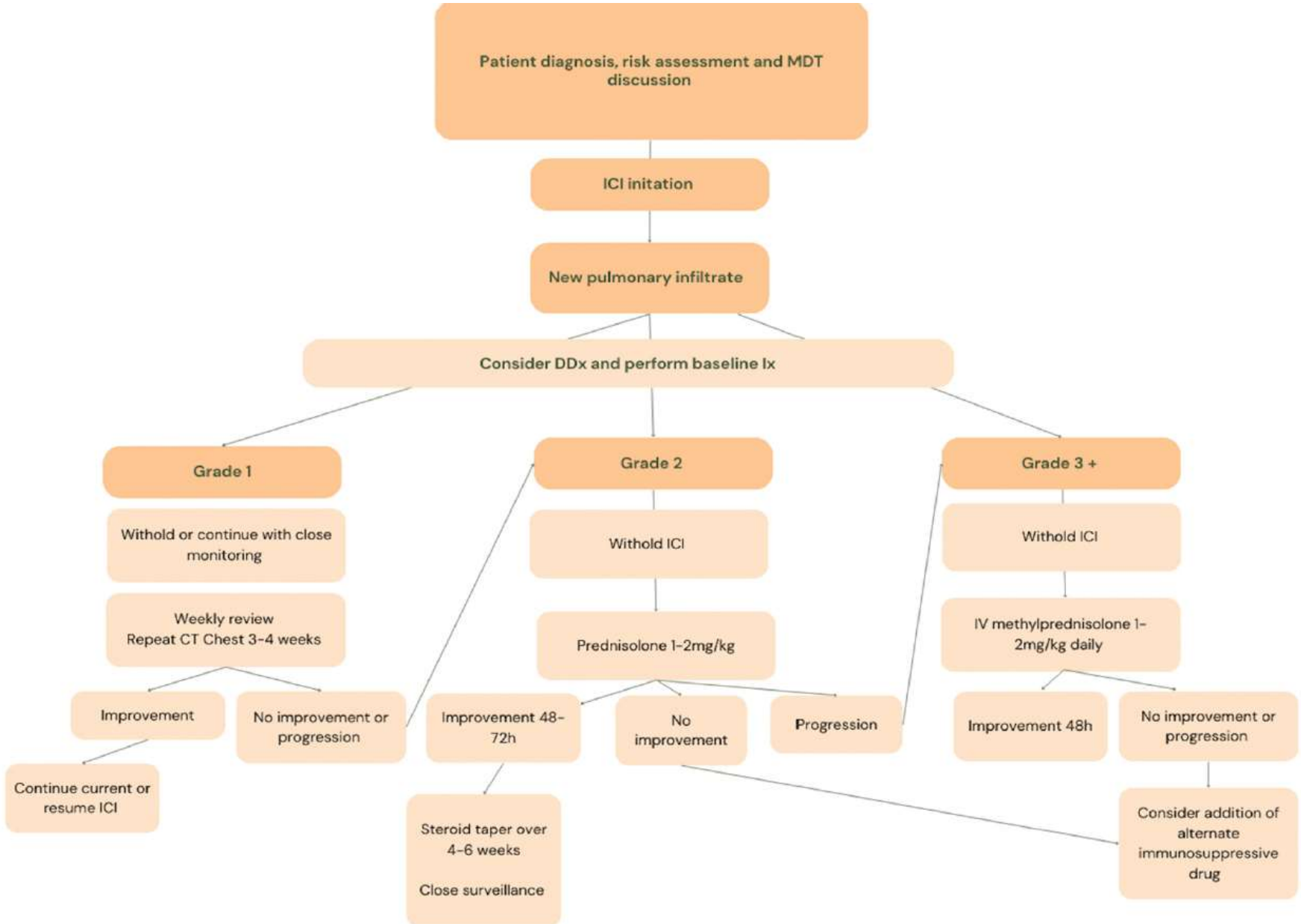
ICI- PNEUMONITIS

MANAGEMENT APPROACH FOR ICI-PNEUMONITIS



- Consider DD and baseline investigations
- ICI- immune checkpoint inhibitors

Adapted from American Society of Clinical Oncology (ASCO) guidelines for managing immune- related adverse events



Haanen, J., et al. (2022). Management of toxicities from immunotherapy: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up. Annals of Oncology, 33(12), 1323-1334

ROLE OF STEROID IN DILD

Author	Drug	Patient Population	Sample Size	Glucocorticoids Dose (Oral or IV)	Response
Mankikian et al. [80]	Amiodarone	DIILD	46	Median dose of 1 mg/kg 15 surviving patients followed and 9 (60%) received glucocorticoids for 3–29 months. All surviving patients successfully had glucocorticoids withdrawn	76% got glucocorticoids but no obvious difference in survival outcomes. Three patients treated for <3 months relapsed and glucocorticoids restarted. No relapse in patients treated for >6 months
Kakugawa et al. [12]	Various	DIILD	47	29 of 47 patients received glucocorticoid therapy. Decision on glucocorticoid therapy was physician-based rather than protocol-based. No dosing information available	None of the patients with a DAD pattern on HRCT improved with glucocorticoid treatment, and DAD group had a 37.5% mortality. 75% of those with OP pattern on HRCT (3 of 4) improved with glucocorticoid treatment. With an NSIP pattern, 45.8% (11 of 24 patients) improved with glucocorticoid treatment. Hypersensitivity pneumonitis (HP) pattern was associated with a 36.4% response to glucocorticoid therapy.
Ki et al. [134]	Bleomycin with cisplatin and vincristine	Cervical cancer patients treated with prior mentioned agents [59]	61 (7 cases of DIILD)	4 with bleomycin injury received glucocorticoid Different regimens within the study. 1 patient who improved received 40 mg/day methylprednisolone, followed by 10 mg daily. 2 acutely ill patients received IV methylprednisolone 500 mg/day × 3 days. 1 patient received 1 mg/kg/day prednisolone, then 0.5 mg/kg	Of these 4 patients, 2 died, 1 improved, 1 non-responder. Insulin-dependent diabetes developed in 2 patients
Kim et al. [105]	Daptomycin	Suspected DIILD	58 (7 definite DIILD cases, 13 probable cases)	No dosing information Definite cases: 5 of 7 received glucocorticoid (1 intravenous) Probable cases: 9 of 13 received glucocorticoid	No deaths 1 required long-term treatment
Rebattu et al. [133]	Gemcitabine with docetaxel	NSCLC patients treated with prior mentioned agents	49 (6 DIILD cases)	6/6 received glucocorticoids	All recovered
Ohnishi et al. [94]	Imatinib	DIILD	27	19/27 received high dose glucocorticoids 5/27 moderate dose glucocorticoids3/27 no treatment	7/27 resolved 16/27 improved 4/27 no improvement
Sharma et al. [59]	Methotrexate	Primary biliary cirrhosis patients treated with methotrexate	43 (6 DIILD cases)	5/6 received prednisolone 60 mg IV daily Duration of intravenous route and glucocorticoids taper unclear	4/5 given glucocorticoids responded, 1 patient died from liver decompensation

Author	Drug	Patient Population	Sample Size	Glucocorticoids Dose (Oral or IV)	Response
White et al. [45]	Everolimus	Advanced renal cell cancer patients treated with everolimus	416 (37 DIILD cases)	16/37 patients received glucocorticoids All 10 patients with grade 3 pneumonitis received glucocorticoids	10 patients with grade 3 pneumonitis who received glucocorticoids 3/10 continued everolimus: 1 died and 2 recovered 7/10 discontinued: 5 recovered, 1 had ongoing disease, 1 died
Tomii et al. [95]	Pemetrexed	Mesothelioma and NSCLC DIILD patients	1586 (10 DIILD cases)	10 cases, all of which received glucocorticoids	5/10 patients deemed glucocorticoids responsive, 1 indeterminate, 4 non-glucocorticoids responders died
Osawa et al. [33]	Panitumumab	Colorectal cancer patients treated with panitumumab	3085 (39 DIILD cases)	No dosing information available	Minimal information on glucocorticoid impact other than statement that most of the 20 patients who died had received glucocorticoids
Yoshii et al. [93]	Irinotecan	Cancer patients treated with irinotecan	8864 (153 DIILD cases, 83 with clinical information)	75/83 patients received glucocorticoids No dosing information available	46/75 of those treated recovered or improved, 5/75 no response, 22/75 died, 2/75 unknown outcome DAD pattern associated with lack of response to glucocorticoids
Liote et al. [73]	Rituximab	DIILD	45	27/45 cases of rituximab DIILD received glucocorticoid. Dosing unclear. Some patients received 1 mg/kg of body weight concomitantly with re-challenge.	No recurrence of rituximab injury in 3 patients receiving re-challenge with rituximab and concomitant 1 mg/kg methylprednisolone Early onset acute presentation: 5 patients all received glucocorticoids, 2 died Late onset chronic presentation in 3 patients who recovered with glucocorticoid therapy Authors recommend longer period of glucocorticoids usage rather than just boluses at each rituximab infusion, and a gradual taper to avoid rebound
Takatani et al. [122]	Various	DIILD		DAD group received median cumulative glucocorticoids dose of 5240 mg, range 1000–9195 mg; NSIP group median of 264, range 0–735 mg; HP group median 415, range 0–4470 mg; OP group median 2722, range 0–7835 mg	Days of oxygen therapy correlated well with cumulative doses of glucocorticoid therapy, i.e., the sicker patients received more glucocorticoids. OP pattern patients showed full recovery with glucocorticoids. No deaths in this group of 34 non-chemotherapy DIILD pts. 11 pts recovered fully without glucocorticoids

Author	Drug	Patient Population	Sample Size	Glucocorticoids Dose (Oral or IV)	Response
Chap et al. [116]	Cyclophosphamide, cisplatin and BCNU	Breast cancer patients treated with prior mentioned	64 (37 cases of DIILD)	37/37 treated with prednisolone 60 mg oral twice daily × 10 days, then 30 mg/day × 1 week, 20 mg/day × 1 week, 15 mg/day × 1 week, followed by 5 mg taper on daily dose each week. Initiation of prednisolone based on scoring system; crackles on lung auscultation = 2, drop in D_{LCO} by >10% from baseline = 3, drop in O_2 saturation ≥4% with 2 min walk = 3, interstitial infiltrates on CXR = 3. Patients with a score ≥6 received prednisolone as above.	Glucocorticoid therapy associated with rapid clinical improvement in "most patients" (absolute numbers not available). 11 patients required prolonged prednisolone therapy (4–8 months), having experienced exacerbation of symptoms when prednisolone reduced to 15–20 mg/day
Hamada et al. [30]	Gemcitabine	pancreatic, lung, urothelial, breast, ovarian	25,924 (428 cases of ILD not verified as DIILD)	363/428 (84%) patients with ILD received either oral or intravenous glucocorticoids	20% of hospitalised DIILD patients with severe disease died, no data on glucocorticoid-treated group outcome versus non-glucocorticoid-treated patients

Infliximab and Intravenous Immunoglobulin Therapy in Treating Patients With Steroid-Refractory Pneumonitis

ClinicalTrials.gov ID NCT04438382

Sponsor ECOG-ACRIN Cancer Research Group

Information provided by Eastern Cooperative Oncology Group (ECOG-ACRIN Cancer Research Group) (Responsible Party)

Last Update Posted 2024-06-13

Terminated

Slow accrual

FUTURE PERSPECTIVE

- How can we develop and validate better biomarkers ?
- What are the optimal dosing strategies for real-world use?
- Should we move towards creating a risk prediction score that integrates age, drug exposures, and comorbidities ?
- Can clinical trials provide conclusive data and help set standardized protocols?

SUMMARY

- Variable latency
- Baseline PFT and DLCO
- HRCT chest if indicated
- FOB BAL- rule out infections
- Bleomycin toxicity can be attenuated by oxygen
- Usually improve with discontinuation
- Role of steroid – individualized

Case Details

- 50 year old male
- Never smoker
- K/C/O DLBCL on R-CHOP regimen since 2023

Last cycle- 13/5/2024

Chief complaints:

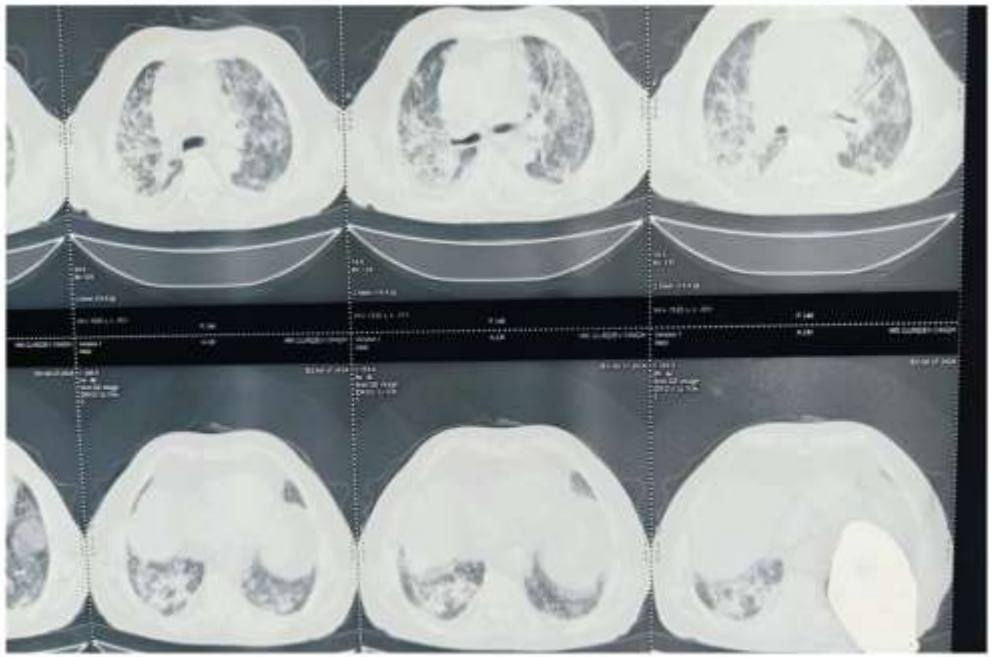
- SOB x 1months
- Cough x 2 weeks

Investigations	
WBC, differential	Blood eosinophilia
Serology	ANA negative
HRCT thorax	Bilateral diffuse patchy GGO with patchy areas of consolidation
Pulmonary Function Tests	Reduced DLCO, Reduced FVC
Selected Microbiological Testing	• Viral - SARS CoV2, CMV : Negative • Sputum Fungal KOH , Gram stain and CBNAAT : Negative
FOB BAL	• Cultures- Inconclusive • BAL galactomannan - neg ▪ BAL- eosinophilia and lymphocytosis

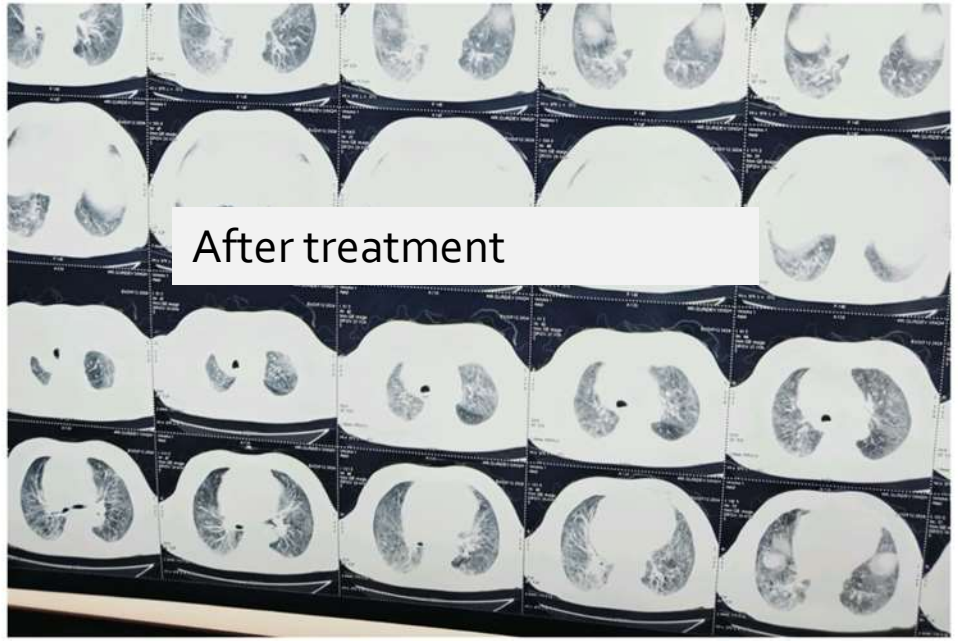
Treatment

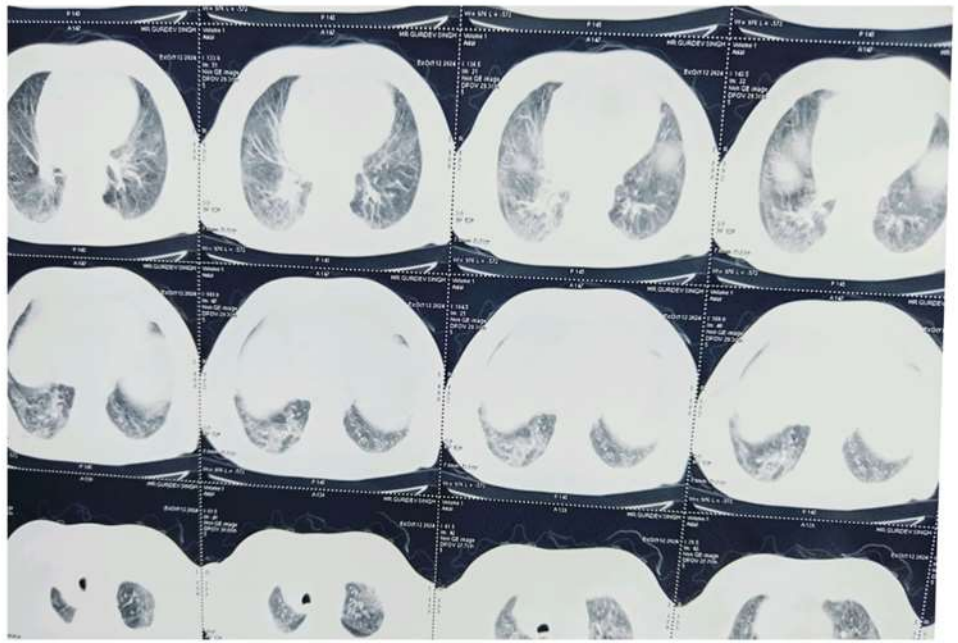
- Probably drug induced ILD- Rituximab>> Doxorubicin (Pneumotox. com search)
- Discontinuation of R-CHOP regimen
- Steroid - Prednisolone 0.75 mg/kg and tapered over 3-6 months.
- Clinical improvement after 3 months
- OUTCOME: Pre and post treatment FVC : 44% and 94%

Before treatment



After treatment





THANK YOU