PULMONARY PEARLS

INDEX

ACR - Lung-RADS reporting and management system

- Category 1: no nodules identified on imaging. The next LDCT recommended is the annual scan
- Category 2: largest solid nodule is <6 mm (risk of malignancy ≤1%). The next LDCT recommended is the annual scan
- Category 3: the largest solid nodules is 6 to <8 mm (risk of malignancy 1%-2%). The next LDCT recommended is 6 months later
- Category 4: the largest solid nodule is ≥8 mm (risk of malignancy 5%-15% for category 4A and >15% for category 4B. On the basis of the probability of malignancy and the clinical characteristics of the individual, the evaluation may include:
    - Follow-up CT in 3 months
    - PET/CT scanning
    - Nonsurgical biopsy
    - Surgical resection

Acute and chronic rejection after lung transplant (LT)

Acute

- May be asymptomatic or have a decrease in the FEV_1, low-grade fever, shortness of breath, or cough
- Usually within the first 6 to 12 months post LT
- It is a histologic diagnosis with lymphocyte predominant inflammatory response (vascular and airway in isolation or combined)
    - Vascular rejection (lymphocytic vasculitis) and acute airway inflammation (lymphocytic bronchiolitis) can be seen independently or may be both present
- Treatment for acute rejection
    - High dose IV methylprednisolone for high grades
    - Adjustment of immunosuppressant regimen for lower grades

Chronic lung allograft dysfunction (CLAD)

- CLAD typically develops after 3 months of LT
- Defined as a persistent decline (≥20%) in FEV_1 when compared with the posttransplant baseline, which persists after 3 months without improvement
- It is a limiting factor in long-term LT survival
    - Leading single cause of death after the first posttransplant year
- Recently, donor-derived cell-free DNA detected in peripheral blood is being used as a sensitive marker for allograft dysfunction
- There are two described CLAD phenotypes:
    - *Bronchiolitis obliterans syndrome (CLAD-BOS)*
        - When the bronchoscopic result for suspected CLAD-BO is nondiagnostic, the term "bronchiolitis obliterans syndrome-BOS" is used
        - Risk factors include acute cellular rejection, especially high grade and recurrent; CMV, particularly pneumonia; other viral infections; primary graft dysfunction; gastroesophageal reflux; and possibly autoimmunity
    - *Restrictive allograft syndrome (CLAD-RAS)*

        - Characterized by upper lobe-predominant fibrotic parenchymal opacities and pleural thickening, sometimes with bronchiectasis and a restrictive defect
            - TLC <90% of baseline or a drop of 10% from baseline
        - Pathologic examination may show alveolar damage; interstitial fibrosis; and interlobular septal and visceral pleural fibroelastosis, with or without obliterative bronchiolitis; and bronchiectasis
        - Risk factors are less well defined, but antibody-mediated rejection or autoimmunity may be a risk factor
- Treatment for CLAD
    - High-dose corticosteroids are of little benefit
    - Azithromycin should be added to the regimen to slow or even slightly improve disease progression
    - The maintenance immunosuppressive regimen should be optimized with tacrolimus and mycophenolate as the preferred combination
    - Other treatment options include montelukast, sirolimus or everolimus, extracorporeal photopheresis, total lymphoid irradiation, rituximab, immune globulins, and antilymphocyte or antithymocyte therapy

Retransplantation may be performed for refractory CLAD, especially CLAD-BOS

Chronic eosinophilic pneumonia (CEP)

Asthma is present in approximately 50% to 75% of patients

- Diagnosis is typically based on the following combination:
    - Subacute dyspnea and cough, chest CT showing predominantly peripheral or pleural-based opacities, and BAL eosinophilia (≥25 percent)
    - Infections (fungal or parasitic) and drug-induced pulmonary eosinophilia need to be excluded. Other differential diagnosis include ABPA, EGPA, and COP
    - Elevated IgE levels in one-half of patients but not in the range usually seen in ABPA
    - Lung biopsy is not necessary unless the BAL does not show eosinophilia, the chest imaging features are atypical, or the patient does not respond promptly to systemic glucocorticoid therapy
- Treatment with corticosteroids
    - Usually with a rapid initial response over 24 to 48 h
    - Slow tapers are required over 6 or more months and up to three-fourths of patients will require ongoing therapy for several years
    - Relapse is common
    - Starting dose
        - Prednisone (or equivalent) 0.5 mg/kg/d x2 weeks after the complete resolution of symptoms and chest imaging abnormalities (usually four to six weeks into therapy)
        - For rapidly progressive disease or respiratory failure methylprednisolone 60 to 125 mg/IVq6h x3-5 days and then transitioning to oral therapy with prednisone as above
    - Maintenance dose

        - Taper Prednisone 0.5 mg/kg/d down to 0.25 mg/kg/d for 8 weeks
        - The optimal duration of therapy is not known. After 3 months some recommend taper prednisone by 5 mg increments every month as tolerated until complete cessation of therapy or a disease flare
    - In refractory cases, high-dose inhaled corticosteroid and biologics have been tried

Common variable immune deficiency (CVID)

Defined as:

- Low level of Immunoglobulins (IgG and or IgM and or IgA)
- Poor response to immunization
- Absence of any other immunodeficiency state
- Characteristics
    - Common infections
        - PNA, rhinosinusitis, GI, mycoplasma UTI, skin herpes zoster/molluscum, meningitis, and encapsulated bacterial sepsis
    - Bronchiectasis and/or granulomatous disease
    - Hepatosplenomegaly
    - Autoimmune dysregulation
        - Idiopathic thrombocytopenia, hemolytic anemia, and RA
            - Requires immunosuppressive therapy
    - Malignancy
- Treatment: IgG either monthly or, if recurrent infections and progressive lung disease occur, more frequently

Congenital lung malformations that may present as cystic or bullous lesions

- Bronchogenic cysts
    - Should be managed with surgical excision because there is potential for malignant degeneration
- Congenital lobar emphysema (CLE)
    - Placental transmogrification of the lung (PTL) is considered a variant
    - Patients who are asymptomatic may be conservatively managed
    - if medical management fails to control symptoms, patients are often referred for surgical bullectomy
- Swyer-James-MacLeod (SJM) syndrome
    - Hyperinflation of one lung or one lobe that is thought to be a postinfectious form of bronchiolitis obliterans
    - Most patients are asymptomatic, but some may develop complications including
        - Bronchiectasis
        - Lung abscess
        - Spontaneous pneumothorax
    - Management is generally conservative

Cryptococcosis

- Cryptococcus neoformans is rare in immunocompetent

    - Found in soil contaminated with pigeon droppings
- In contrast, Cryptococcus *gattii* can be found in immunocompetent pts
    - Associated with eucalyptus trees
- CNS and skin involvement are common in patients with disseminated cryptococcosis
- The diagnosis requires confirming Cryptococcus
    - Cryptococcal antigen testing of CSF and/or serum provides presumptive evidence for cryptococcosis
        - PCR has high sensitivity and specificity
    - Cultures - high-power field of Grocott methenamine silver stain
    - Tissue biopsy - budding yeast organisms
- Treatment
    - Amphotericin B plus flucytosine
    - Hydrocephalus required serial LPs until 2 days of pressure normalization and finally a VP shunt
    - Immunosuppressive management should include stepwise reduction of immunosuppressives including corticosteroids
    - Corticosteroids can be considered:
        - For immune reconstitution inflammatory syndrome with CNS inflammation and increased intracranial pressure
        - Cryptococcomas with evidence of mass effect and surrounding edema
    - Patients who are immunocompromised with pneumonia with associated CNS or dissemination and/or severe pneumonia (eg, ARDS) should be treated as if they have CNS disease
- Fluconazole for 6 to 12 months
    - Mild to moderate symptoms
    - Absence of diffuse pulmonary infiltrates
    - Absence of severe immunosuppression
    - Negative results of diagnostic evaluation for dissemination can be treated with oral

Cystic fibrosis

- *F508del* mutations is the most common mutation
- Triple combination therapy with elexacaftor-tezacaftor-ivacaftor is preferred
    - Fewer adverse effects, drug-drug interactions, and improve lung function with greater improvement in FEV_1
    - Corrects the function of the abnormal cystic fibrosis transmembrane conductance regulator protein produced by the patient
    - It can normalize sweat chloride test results, produce weight gain, and improve quality of life to a greater degree than can treatment with ivacaftor monotherapy, lumacaftor plus ivacaftor, or tezacaftor plus ivacaftor, or ivacaftor monotherapy

Cytochrome P450

Example of medications metabolized by P450

- CNI
- Nintedanib

Examples of strong inhibitors

- Azoles and many antiviral agents
- Paxlovid
    - Decrease dose of CNI and Nintedanib when initiating or increasing the dose of the azoles
    - Paxlovid: recent recommendations now allow for use of this agent with very careful monitoring of CNI levels and a significant CNI dose reduction and/or sometimes a short period of discontinuation

Examples of inducers

- Rifamycin/Rifampin, phenytoin, the cystic fibrosis transmembrane conductance regulator modulators, and phenobarbital
    - Increase in the CNI dose in addition to close monitoring of blood levels would be required

Dupilumab pearls

- Improvement in lung function after 2 weeks and statistically significant at week 12
    - Greater benefits in patients with higher baseline levels of eosinophils and FENO >25
- Transient elevation of AEC with levels generally returning to baseline or lower over time
    - Usually not been associated with clinical symptoms, nor does it affect efficacy, and therefore dose adjustment or discontinuation of treatment is not necessary
    - Expert opinion guidelines suggest
        - Repeating an AEC every 4 weeks for AEC >1,500
        - Stopping dupilumab for those with an AEC >5,000 or if there is evidence of hyper eosinophilic organ infiltration (such as heart dysfunction, neurological symptoms, or dyspnea)
    - Evaluation for EGPA is also appropriate when such eosinophil counts persist, especially if associated with new pulmonary symptoms or infiltrates
    - Although there are no standard guidelines, patients with a baseline eosinophil level ≥ 300 should be screened for nonallergic causes, including *Strongyloides* infection (even without symptoms) before considering biologic therapy
- Dupilumab leads to a significant reduction in blood levels of total and allergen-specific IgE
    - Other biologic agents indicated for asthma with an eosinophilic phenotype cause a reduction in blood eosinophils after several weeks of treatment, with a variable response to IgE levels
- Indications as an add-on maintenance treatment for pts with moderate to severe asthma
    - Eosinophilic phenotype, poorly controlled with a medium- to high-dose inhaled corticosteroid in combination with an additional controller medication, with a pretreatment blood eosinophil count greater than 150
    - Oral corticosteroid-dependent asthma
- Also indicated atopic dermatitis and chronic rhinosinusitis with nasal polyps and eczema

EVALI

- Vaping within the last 90 days
- Pulmonary infiltrates

- Exclusion of alternative causes
    - Heart failure, rheumatologic or neoplastic lung disease, and pulmonary infection
    - BAL is not routinely recommended
    - When done, lipid-laden macrophages are common
- Treatment
    - Empiric Antibiotics pending the results of initial evaluation and response to therapy
    - Steroids for pts with worsening symptoms and hypoxemia
        - Methylprednisolone 1 mg/Kg/d and taper over 5 to 10 days

Galactomannan (GM)

- Positive in aspergillus, cryptococcus, fusarium, and histoplasma
- False-positive
    - Some bacterial infections (some strains of *Pseudomonas aeruginosa*)
    - Amoxicillin-clavulanic acid and piperacillin/tazobactam
    - Hemodialysis using cellulose membranes
    - IV immunoglobulin
    - Some albumin compounds, use of cellulose filters for IV administration of certain infusions, and gauze used to pack serosal surfaces
- Decrease sensitivity
    - Concurrent use of antifungal treatment, recipients of solid organ transplant, and other immunocompromised populations, and disease limited to the airways
- Mucormycosis negative results for both BDG and GM
    - Culture often yields no growth, biopsy is needed
    - Surgical debridement and lipid formulations of amphotericin B

1,3-β-d-glucan (BDG)

- 1,3-β-d-glucan (BDG)
    - Positive in candida, aspergillus, and PJP
        - In PJP
            - BDG has become important in the suspected/presumptive diagnosis of PJP in those too unstable to undergo bronchoscopy with a good sensitivity and a high NPP
            - LDH levels are usually not as high in patients without HIV
    - Negative in cryptococcosis and blastomycosis

Ground glass nodules

- Pure lipidic
    - Growth of the ground-glass component alone does not suggest a malignancy is becoming invasive and thus does not require more aggressive management
        - Smaller than 6 mm do not require additional testing or monitoring
        - Larger than 6 mm: chest CT scan in 6 to 12 months and then every 2 years for 5 years if it remains stable
- Part solid
    - Should be managed based on the size of the solid component

        - Chest CT in 6 months if the solid component is <6 mm
        - Chest CT in 3 months if the solid component is 6 to 8 mm
        - If the solid component is >8 mm management should follow solid nodule guidelines
- Cigarette smoking is not considered a risk
- Causes other than asbestos
    - BAP1 pathogenic mutation
    - Exposure to ionizing radiation to supradiaphragmatic fields in the treatment of malignancy (Hodgkin and non-Hodgkin lymphoma, testicular cancer)
- Subtypes: epithelioid, sarcomatoid, and biphasic
- Several biomarkers are selectively elevated but not routinely used in the diagnosis
    - Soluble mesothelin-related peptides, fibulin-3, and osteopontin

Hypoxia altitude simulation test (HAST) – COPD pts

- Resting SpO_2 >95% and dyspnea mMRC <3 on RA in-flight supplemental oxygen is not needed
- Resting SpO_2 <92% on RA should receive in-flight supplemental oxygen
- Indications for preflight 6 MWT
    - Resting SpO_2 of 92-95% on RA
    - Resting SpO_2 greater than 95% on RA and dyspnea mMRC ≥3
        - SpO_2 ≥84%, no in-flight supplemental oxygen is needed
        - SpO_2 <84% a HAST is recommended
- Alternatively, the British Thoracic Society (BTS) guidelines suggest providing in-flight supplemental oxygen or proceeding to HAST in patients with SpO_2 less than 95%

Idiopathic inflammatory myositis (dermatomyositis, polymyositis, or antisynthetase syndrome)

- ANA often negative
- ILD/OP may progress to PF-NSIP
- Antisynthetase syndrome
    - Myositis-specific antibody PL-7 confirms the diagnosis
    - Unlike classical dermatomyositis is less often associated with malignancy
- Treatment
    - First line - Corticosteroids often result in improvement, most patients require multimodality immunosuppressive therapy
    - Second line - MMF, AZA, Cyclophosphamide
    - Add on therapy – Rituximab, IVIG, tacrolimus

ILD lung transplant indications

To improve quality of life, functional capacity, and survival

- Dyspnea – functional limitation
- Need for supplemental O2
- Abnormal PFTs
    - FVC <80%
    - DLCO <40%
- Associated pulmonary hypertension

- Failure to improve after a trial of medical management

COPD lung transplant indications

To improve quality of life and functional capacity

- Progressive disease, BODE index >7 and not candidates for lung volume reduction with at least one of the following:
    - Hospitalization for exacerbation with acute hypercapnia (PaCO2 > 50 mmHg)
    - FEV1 < 20% and either DLco <20% or homogeneous emphysema
    - Associated pulmonary hypertension and/or cor pulmonale despite O2 therapy

LAM treatment

- Supportive care, supplemental oxygen, bronchodilators, pulmonary rehabilitation, and sirolimus
    - Sirolimus should be started:
        - Patients with symptoms and/or abnormal lung function (FEV_1 <70% predicted)
        - Evidence of rapidly progressive disease
        - Chylous effusions
        - AMLs
    - Avoidance of pregnancy and estrogen-containing medications
    - Birth control medications should be progesterone based
- Eventually may require lung transplantation because of progressive respiratory failure
    - The outcomes appear to be comparable with or better than in patients receiving transplants for other lung diseases
    - Disease recurrence is described

Leptomeningeal disease with lymph node and pulmonary involvement

- Mycosis (eg., criptococosis, coccidioidomicosis)
- TB
- Sarcoidosis
- Malignancy
    - Most common with breast carcinoma, lung carcinoma, and melanoma
- Primary CNS lymphomas can also cause leptomeningeal involvement
    - Most common is B-cell lymphoma
    - Often in immunocompromised pts
    - Transient and rapid responses in patients treated with corticosteroids
        - Performing a biopsy before corticosteroid administration is recommended
- Others

Lung abscess

- Percutaneous catheter drainage or transbronchoscopic catheter drainage may be considered
    - Pts who do not respond to antibiotic therapy, depending on the location of the abscess
        - Peripheral/abutting the pleura vs central
    - Should not be attempted prior to antibiotic therapy
- Surgical intervention is rarely indicated for pts who fail to improve with antibiotic therapy or develop a complication during treatment (eg, bronchopleural fistula)

    - Mortality with surgical intervention is as high as 15% to 20%, and surgery should not be considered before a prolonged trial of antibiotic therapy

Mesothelioma BAP1 pathogenic mutation

Is associated with an increased risk for a variety of cancers

- Malignant mesothelioma
    - Can occur with no exposure to asbestos
        - Tend to be less aggressive
- Uveal and cutaneous melanoma
- Clear cell renal cell carcinoma
- Other less common
    - Basal and squamous cell carcinomas of the skin
    - Meningioma
    - Bladder cancer
    - Cholangiocarcinoma
    - Lung cancer
- Screening for *BAP1* mutations
    - Families with three or more of the most common of these cancers and considered in first-degree relatives of those with mutations
    - Annual eye and skin examinations
    - MRI of the chest, abdomen, pelvis, and breast every other year is suggested as screening protocol

Multiple pulmonary sites of cancer

They fall into one of four patterns:

- Separate primary lung cancers
- Separate tumor nodules of the same cancer
- Multiple tumors with prominent ground-glass features on imaging or lepidic histologic features
- Diffuse pneumonic pattern

Distinguishing second primary cancers from separate tumor nodules:

- Requires histologic confirmation
- Features that favor separate tumors include:
    - Differences in their imaging appearance
    - Different rate of growth
    - Absence of regional lymph node involvement)
    - Presence of different molecular biomarker patterns
- Separate TNM classifications are assigned to each tumor
    - Separate tumor nodules of the same cancer are staged as one cancer
        - T3 is applied when the tumors are in the same lobe
        - T4 when in separate lobes of the same lung
        - M1a when in separate lungs

Multiple tumors with a prominent ground-glass component:

- They have become more common and their behavior has shaped thoughts about staging and treatment

- Tend to behave indolently with excellent survival and a low rate of regional or distant spread
- Each tumor site usually behaves independently

Diffuse pneumonic-type presentations:

- Are associated with more aggressive disease and poorer prognosis though they are still less likely to spread to nodal or distant sites
- They are usually invasive mucinous adenocarcinomas

Neuromuscular restrictive process

- Parameters to guide initiation of NIV should be assessed frequently (usually at 3-month intervals)
- Indications for NIPPV
  - Early
    - VC <50%
    - MIP or MEP <60
    - Orthopnea
    - Abnormal nocturnal oximetry
  - Late
    - Awake dyspnea
    - SpO_2 <95% on RA
    - $PaCO_2$ >45
- Patients with neuromuscular diseases may be unable to perform PFTs
  - Inability to maintain a seal around the mouthpiece confounds performance of the VC and MIP
  - Maximal sniff inspiratory pressure (SNIP) is an attractive alternative
    - A manometer is placed in an occluded nostril while the patient makes a sniff through the contralateral, nonoccluded nostril
    - The specificity and sensitivity of the test compare favorably with VC and NIV
    - SNIP <40 cm H_2O is the threshold for recommending initiation of NIPPV

Nocardia treatment

- Trimethoprim-sulfamethoxazole, meropenem and amikacin given intravenously
- After 6 weeks of IV therapy, the regimen may be switched to oral agents
  - Trimethoprim-sulfamethoxazole, minocycline, and/or amoxicillin-clavulanate
- The duration of treatment is 6 to 12 months

Persistent cough- symptomatic management

- Benzonatate
- Gabapentin
  - Particularly can be useful in ILD and sensory neuropathic cough
  - High doses are often required and can limit treatment owing to adverse effects that most commonly include fatigue, dizziness, confusion, dry mouth, and nausea
    - 100 mg q8h starting dose; increased the dose by 100 mg every 3 days thereafter until 300 mg q8h or the onset of intolerable drug side effects

- Codeine if refractory to treatment of underlying cause treatment with benzonatate and/or gabapentin
- Multimodality speech therapy
    - Cough suppression techniques
    - Vocal hygiene
    - Psychoeducational counseling to treatment

Persistent dyspnea after COVID-19

- Interstitial fibrosis
- Thromboembolic disease
- Reduced cardiac function from myocarditis
- Impairment of O_2 extraction
    - Microcirculation or mitochondrial dysfunction
- Weakness of diaphragmatic contraction
- Cardiovascular deconditioning

Reduced perception of lung expansion, possibly because of neuropathy

PPHTN

- Can improve with liver transplant
    - Approximately one-half of patients with PPHTN have posttransplant resolution of PPHTN and are able to discontinue PAH therapy
- MELD exception criteria
    - mPAP must be less than 35 mm Hg after PAH-specific therapy
- Acute PH can develop immediately after TIPS

Pulmonary alveolar proteinosis (PAP)

Autoimmune PAP with development of anti-GM-CSF autoantibodies resulting in blocking the regulation of macrophages by GM-CSF and accumulation of surfactant

- Serum GM-CSF levels are typically normal
- The autoantibodies can be shown by a commercially available test that is both highly sensitive and specific
- Daily administration of GM-CSF by inhalation can improve the course of this disease
- Inhaled molgramostim for GM-CSF augmentation is available for off-label use at the time

Pulmonary lymphoproliferative disorders

- LIP
- CVID
    - Granulomatous and lymphocytic interstitial lung disease described in patients may be a form of LIP which may be related to human herpesvirus type 8
- Follicular bronchiolitis (thought to be closely related to LIP)
- Lymphoma
- Lymphomatoid granulomatosis

- Bronchocentric granulomatosis
- IgG4-related disease

PVOD/PCH

- Compared with others PAH has a more fulminant course and a worse prognosis
- The diagnosis is strongly suggested by:
    - Pulmonary interstitial edema, intralobular and interlobular septal thickening, and ground-glass opacities in the absence of left atrial hypertension
    - Mediastinal lymphadenopathy, pleural effusions, and pericardial effusion may also be seen
    - Hemoptysis, usually nonmassive, may occur, and hemosiderin-laden macrophages are frequently seen in BAL

Silicosis

- The earliest and most characteristic findings are small peri lymphatic nodules and mediastinal lymphadenopathy (eggshell pattern).
- Can progress to progressive massive fibrosis (PMF) and emphysematous changes
- Diagnosis of chronic silicosis does not rely on a biopsy. It is based on three elements:
    - Occupational exposure
    - Chest imaging
    - Absence of an alternative diagnosis
- When biopsy is done birefringent crystals are visible in most cases

Spontaneous bacterial empyema (SBEM) - "spontaneous bacterial pleuritis"

- Defined as spontaneous infection of a preexisting hepatic hydrothorax
    - It can occur in the absence of spontaneous bacterial peritonitis (SBP)
    - Few cases have been reported in noncirrhotic patients
- Diagnosis
    - Pleural fluid neutrophil count is >500/µL with negative culture or >250/µL with a positive fluid culture
    - Pleural fluid typically appears yellow and not purulent as in the case of a parapneumonic empyema and usually transudative consistent with a hydrothorax