Drug & Radiation induced lung diseases

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• Drug-induced lung diseases have been a challenge since the dawn of modern medicine

• 1880, William Osler suggested a pathophysiologic relationship of pulmonary edema associated with opiate exposure

• 1972, Edward Rosenow identified 20 drugs that clearly caused pulmonary toxicity

Rosenow EC. Ann Intern Med 1972; 77:977–991

• Cooper et al expanded the list to 37 drugs a decade later
• Presently > 350 drugs have been implicated in causing pulmonary manifestations

• Number of drugs will continue to grow as new agents & biological response modifiers are developed

• Involve all components of respiratory system
• Epidemiology of DILD is not firmly established as it is diagnosis of exclusion

• No pathognomonic clinical, laboratory, physiologic, radiographic, or histologic findings

• Most reactions are idiosyncratic without any clear relationship to dose / time of exposure

• Drugs can cause toxicity years after exposure → cyclophosphamid
• Risk factors poorly defined
• Confounding variables
  – Use of other drugs
  – Oxygen
  – Radiation therapy
    can cause pulmonary injury or have interactive effects & hamper diagnosis
• Rechallenge with implicated drug is rarely performed as effective alternative agents are usually available

• Thorough drug exposure history, high index of suspicion & use of systematic diagnostic is required
• Management is largely supportive

  – Therapy with implicated drug is withdrawn
  – Trial of corticosteroids is considered if
    • Significant symptoms
    • Gas-exchange abnormalities

• Scientific basis for corticosteroids is supported by anecdotal reports w/o well designed controlled studies
<table>
<thead>
<tr>
<th>No.</th>
<th>Condition</th>
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<tbody>
<tr>
<td>1.</td>
<td>Chronic pneumonitis/fibrosis*</td>
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<tr>
<td>2.</td>
<td>Hypersensitivity-type lung disease*</td>
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<tr>
<td>3.</td>
<td>Acute noncardiogenic pulmonary edema*</td>
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<td>4.</td>
<td>Bronchiolitis obliterans with organizing pneumonia</td>
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<td>5.</td>
<td>Alveolar hypoventilation</td>
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<td>6.</td>
<td>Bronchospasm</td>
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<td>7.</td>
<td>Cough</td>
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<td>8.</td>
<td>Concentric bronchiolitis obliterans</td>
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<td>9.</td>
<td>Pleural effusions</td>
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<td>10.</td>
<td>Venous thromboembolism</td>
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<td>11.</td>
<td>Pulmonary vasculitis</td>
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<td>12.</td>
<td>Pulmonary hypertension</td>
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<td>13.</td>
<td>Drug-induced SLE</td>
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<td>14.</td>
<td>Alveolar hemorrhage</td>
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<td>15.</td>
<td>Pulmonary renal syndrome</td>
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<td>16.</td>
<td>Alveolar proteinosis</td>
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<tr>
<td>17.</td>
<td>Mediastinal abnormalities (e.g., adenopathy, lipomatosis, or mediastinitis)</td>
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<tr>
<td>18.</td>
<td>Panlobular emphysema</td>
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<td>19.</td>
<td>Pulmonary calcinosis</td>
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<tr>
<td>20.</td>
<td>Pseudosepsis syndrome</td>
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</tbody>
</table>

*Most common pulmonary manifestations.
**Chronic Pneumonitis/Fibrosis**

- Most common manifestations

- Present with insidious onset of cough & dyspnea

- Weight loss & clubbing may also be present → possibility of an underlying malignancy or IPF
• **CXR & HRCT:**
  - Reticular infiltrates - in basilar subpleural regions and progressing to diffuse disease

• **PFTs**
  - Reduced lung volumes & DLCO
  - Arterial hypoxemia at rest / with exercise
Table 2. Some Drugs That Cause Chronic Pneumonitis/Fibrosis

<table>
<thead>
<tr>
<th>Chemotherapeutic Agents</th>
<th>Nonchemotherapeutic Agents</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Azathioprine</td>
<td>• Amiodarone*</td>
</tr>
<tr>
<td>• BCNU</td>
<td>• Anti-TNF-α-targeted therapy</td>
</tr>
<tr>
<td>• Bleomycin*</td>
<td>• Cocaine</td>
</tr>
<tr>
<td>• Busulfan</td>
<td>• Gold</td>
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<tr>
<td>• Chlorambucil</td>
<td>• Heroin</td>
</tr>
<tr>
<td>• Cyclophosphamide</td>
<td>• Methysergide</td>
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<tr>
<td>• Fludarabine</td>
<td>• Nitrofurantoin</td>
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<tr>
<td>• Gemcitabine</td>
<td>• Penicillamine</td>
</tr>
<tr>
<td>• 6-Mercaptopurine</td>
<td>• Phenytoin</td>
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<tr>
<td>• Methotrexate</td>
<td>• Sirolimus</td>
</tr>
<tr>
<td>• Mitomycin C</td>
<td>• Statins</td>
</tr>
<tr>
<td>• Taxanes (paclitaxel/docetaxel)</td>
<td>• Sulfasalazine</td>
</tr>
<tr>
<td>• Tyrosine kinase inhibitors (imatinib)</td>
<td>• Tocainide</td>
</tr>
</tbody>
</table>

*Most commonly implicated.
Hypersensitivity-Type Lung Disease

- Any drug can cause reaction with respiratory symptoms associated with PIE
- Methotrexate & Antibiotics (β-lactam & sulfa-containing)
- Patients can present
  - Acute onset → Loeffler syndrome - cough, dyspnea, fever, rash, myalgias, peripheral eosinophilia, and fleeting infiltrates
  - Subacute → CEP as low-grade fever, night sweats, nonproductive cough & weight loss
- Diagnosis → challenging as peripheral eosinophilia not seen in every pt
- FOB with BAL & biopsy or prompt response to corticosteroids favours
- Prognosis is favorable with a mortality rate of 1%
Noncardiogenic pulmonary edema

• No. of drugs causes NCPE
• Acute dyspnea & nonproductive cough
• CXR - diffuse acinar and/or ground-glass infiltrates
• Histopathology can be similar to ARDS
• Mechanisms
  – ↑ filtration coefficient of respiratory membrane → making it more permeable
  – Depress CNS resulting in neurogenic PE
  – Idiosyncratic reaction within hours of absorption

• Prognosis depends on offending agent
  – overdose of salicylates is potentially reversible
  – carmustine-induced generally have a poor prognosis
Cryptogenic Organizing Pneumonia

• Presentation → cough, dyspnea & crackles on physical examination

• CXR - patchy airspace infiltrates

• PFT - mixed obstructive and restrictive defect
• Gold and penicillamine – used for management of RA

• Difficult to distinguish drug-induced COP from underlying CVD

• Management:
  – High clinical suspicion
  – Lung biopsy
  – Prompt withdrawal of therapy
  – Administration of corticosteroids

• Outcome is generally favourable
Alveolar Hypoventilation

• Drugs that induce respiratory depression or block respiratory muscle function

• Pulmonary or neuromuscular disorders are prone to develop acute hypercarbic RF
• Aminoglycoside-induced neuromuscular blockade → rare potentially life-threatening → exposed to neomycin, streptomycin, tobramycin, gentamicin, amikacin, kanamycin, and netilmicin

• Risk is ↑ in presence of
  – Disease / drug that promotes neuromuscular blockade
  – ↑ aminoglycoside drug levels
  – Hypomagnesemia
  – Hypocalcemia

• Mx requires high clinical suspicion & withdrawal of drug to avoid further RF
Bronchospasm

- Presentation: wheezing, cough, dyspnea
- Spirometry $\rightarrow$ airways obstruction
- Mechanism varies with agent
- Asthma $\rightarrow$ $\beta$-adrenergic blockers induce bronchospasm within minutes by inhibition of adrenergic bronchodilator tone
- Any route of administration can induce bronchospasm
• Aspirin → mediated by an enhanced 5-lipoxygenase pathway
  – production of bronchoconstricting cysteinyl leukotrienes
  – reduction in bronchodilating prostaglandins E2

• Dipyridamole → augments levels of adenosine → bronchoconstrion

• Gold / penicillamine → irreversible airways obstruction due to concentric bronchiolitis obliterans
Isolated Cough

• Most common manifestations of DILD

• Mechanism → vagus nerve-mediated reflex caused by chemical & mechanical stimuli in upper & LRT

• ACE inhibitors → 10% of patients induce isolated nonproductive cough without associated bronchospasm / parenchymal disease

J Respir Dis 1997; 18:762–768
Pleural Effusions

• Less common as compared to parenchymal
• Acute onset seen as part of
  – hypersensitivity reaction after exposure to amiodarone, methotrexate, and nitrofurantoin
  – SLE-like reaction
• Anticoagulants → induce acute hemorrhagic effusion
• Chronic pleural effusion
  – Long-term exposure to drugs that induce DHT response (methotrexate / procarbazine)
  – Association with development of interstitial pulmonary inflammation/fibrosis (busulfan / methotrexate)
## Pulmonary Vascular Disease

### Table 9. Some Drugs That Cause Pulmonary Vascular Disease

<table>
<thead>
<tr>
<th>Complication</th>
<th>Chemotherapeutic Agents</th>
<th>Nonchemotherapeutic Agents</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thromboembolic disease</td>
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<td>Estrogens/hormonal treatment</td>
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<td>Phenytoin</td>
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<td></td>
<td>Steroids</td>
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<td>Pulmonary hypertension</td>
<td>Mitomycin</td>
<td>Aminorex (recalled)</td>
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<td></td>
<td>IL- 2</td>
<td>Amphetamines</td>
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<tr>
<td></td>
<td></td>
<td>Dextenfluramine (recalled)</td>
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<td></td>
<td></td>
<td>Fenfluramine (recalled)</td>
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<tr>
<td></td>
<td></td>
<td>L-tryptophan (recalled)</td>
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<tr>
<td></td>
<td></td>
<td>Oral contraceptives</td>
</tr>
<tr>
<td>Vasculitis</td>
<td>Busulfan</td>
<td>Cocaine/heroin</td>
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<tr>
<td></td>
<td></td>
<td>Nitrofurantoin</td>
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<td></td>
<td></td>
<td>Zafirlukast/montelukast</td>
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<tr>
<td>Veno-occlusive disease</td>
<td>Bleomycin</td>
<td>Oral contraceptives</td>
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<tr>
<td></td>
<td>Busulfan</td>
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<tr>
<td></td>
<td>Mitomycin</td>
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</tbody>
</table>
Miscellaneous Drug-Induced Pulmonary Reactions

**lupus erythematosus**

- SLE accounts for 5 to 12% of all cases
- 90% caused by Hydralazine, Procainamide, INH, Penicillamine & Quinidine
- Anti TNF targeted therapy (etanercept, infliximab, & adalimumab)
- Hydralazine & INH - SLE occur more frequently in slow acetylators
- 20% of patients receiving doses of 400 mg/d of Hydralazine develop SLE
• Procainamide-induced SLE is time related
  – 50% develops +ve ANA in ~3 months
  – nearly all patients by 1 year

• Drug-induced SLE - negative for dS DNA

• CXR → PE, atelectasis, diffuse interstitial & alveolar infiltrates
• Alveolar hemorrhage syndrome is not a feature

• Drug withdrawal results in prompt resolution of symptoms within days
• CS occasionally required for symptomatic relief
Alveolar hemorrhage and hemoptysis

• Penicillamine can cause pulmonary-renal syndrome similar to Goodpasture syndrome
• Oral anticoagulants can induce spontaneous pulmonary hgs with in days to years
• Abciximab → Ab directed against platelet glycoprotein IIb/IIIa receptor can cause severe alveolar Hgs

• Relatively rare complication [0.3%]
• Presentation within hrs to 2 days after the first dose

Chest 2001; 120:126–131
• Bevacizumab → monoclonal Ab against VEGF can result in fatal pulmonary hemorrhage
  

• Drug therapy withdrawal is usually sufficient in anticoagulant induced bleeding

• Role of factor VIIa is not established

• DAH with extensive or persistent bleeding, or evidence for renal failure → CS or immunosuppressive agents

Mediastinal abnormalities

- **Phenytoin** can induce a pseudolymphoma syndrome → a/w peripheral & rarely mediastinal adenopathy

- **Methotrexate** → transient hilar adenopathy during hypersensitivity-type response which regresses 1 to 2 weeks after drug withdrawal

- **Corticosteroids** → Mediastinal fullness due to lipomatosi

- Mediastinitis associated with fever & chest pain → rarely seen after esophageal variceal **sclerotherapy**
• Other rare pulmonary adverse drug effects reported:
  
  – Busulfan-induced alveolar proteinosis
  – Methylphenidate-induced panlobular emphysema
  – Pulmonary parenchymal Ca deposition associated with antacids, calcium, high-dose vitamin D

• Long-term salicylate ingestion can cause a pseudosepsis syndrome
Chemotherapy-Associated Pulmonary Toxicity

- Azathioprine - purine analog that inhibits DNA synthesis
- Immunosuppressive agent in Tt of IPF & organ transplantation

- Mercaptopurine → active metabolite of azathioprine & is an antineoplastic agent

- About 1% cases causes pulmonary fibrosis, hypersensitivity-type reactions/PIE or DAD
BCNU

- Extensively studied member of nitrosourea
- Active against various neoplasms including CNS as it can cross blood-brain barrier
- Causes IPF & granulomatous inflammation that can progress after drug withdrawal

- Promotes oxidant-induced lung injury by inhibiting glutathione reductase
- Cytotoxic changes are characterized by
  - Alveolar T2 hyperplasia and dysplasia
  - Fibroblastic foci of proliferation
  - Interstitial fibrosis
• Symptom onset highly variable ➔ days to as many as 17 yr.
• Insidious onset of nonproductive cough dyspnea
• CXR ➔ reticular nodular interstitial infiltrates
• Risk factors include ➔ total dose, other agents & preexisting lung disease
• Incidence
  – high-dose (1,500 mg/m2) ➔ 20 to 50%
  – low-dose ➔ 1 to 5%
• Cyclophosphamide & radiation ↑ risk without synergistic effect
• Mortality rate nearly 90% & Corticosteroid therapy no role in prevention
Bleomycin

- Cytotoxic antibiotic isolated from *Streptomyces verticillus*
- Used in head & neck carcinomas, germ-cell tumors, Hodgkin and NHL
- Accumulates in skin & lung → skin ulcerations & PF

- Overall
  - Incidence 10% (3 to 40%)
  - Fatal in 1 to 2%
- Binds to intracellular iron in alveolar epithelial and vascular endothelial cells & generates highly ROS (hydroxyl radicals) in presence of O₂
• 3 major clinical manifestations
  – chronic interstitial fibrosis
  – hypersensitivity-type disease
  – COP

• Interstitial fibrosis is seen in approximately 11%
• Risk factors for the development of bleomycin induced pulmonary toxicity include
  – Total dose: incidence of 3 to 5% - 300 U but 20% - 500 U
  – Oxygen: synergistic toxic interaction even yrs after exposure
    FiO$_2$ of pt who have ever received bleomycin should be kept 25%
  – Radiation: ↑ risk even years after exposure
  – Age: > 70 years
  – Abnormal renal function
  – Concurrent use of other cytotoxic agents : cyclophosphamide, doxorubicin, G-CSF, methotrexate, and vincristine
Busulfan

- Alkylation agent → Ch myeloproliferative disorders
- First chemotherapeutic agent implicated in causing chronic pneumonitis/pulmonary fibrosis
- Synergistic damage with O₂ / radiation / cytotoxic drugs
- Incidence
  - Symptomatic pulmonary fibrosis is ~ 4 to 5%
  - Asymptomatic - up to 46%
- A threshold dose has not been established

- C/F: insidious onset > 3 years after initiating therapy → cough, dyspnea, fever, malaise, weight loss
- PFT - Restrictive /↓ Dlco
• **CXR:**
  - Diffuse interstitial and alveolar infiltrates with a basilar predominance
  - Occasionally → pleural effusion / nodular densities
  - Normal
• Mx → drug withdrawal & corticosteroids

• Prognosis is poor with mortality rate ranging from 50 to 80%

• Alveolar proteinosis has also been reported after exposure to busulfan

• Does not respond to therapeutic BAL
Cyclophosphamide

- Incidence of adverse pulmonary effects is 1%
- Pathogenesis not established - likely to be oxidant-mediated

- Metabolized → 2 active agents - phosphoramide mustard & acrolein both of which reduce hepatic glutathione stores
- Chronic pneumonitis and/or fibrosis most common clinical manifestations
• Symptoms → 2 weeks to 13 years, without any clear dose relationship

• Synergistic toxicity in patients receiving radiation therapy / cytotoxic agents

Cancer 1985; 55:57–60

• Cyclophosphamide-induced PF present with B /L pleural thickening without clubbing & “Velcro” crackles

• Prognosis is generally poor → mortality rate approaching 50%

Am J Respir Crit Care Med 1996; 154:1851–1856
Methotrexate

• Incidence - 7% for high-dose / 2 to 3% with low-dose
• No clear dose relationship over a broad range (40 to 6,500 mg)
• Clinical manifestations:
  – hypersensitivity-type disease (most common)
  – chronic pneumonitis/fibrosis
  – COP
  – acute chest pain
  – Noncardiogenic pulmonary edema
  – acute pleurisy/pleural effusions
  – bronchospasm
• Hypersensitivity-type reactions → 10 d to 4 mo
• Fever, cough, dyspnea, arthralgias & skin rash
• CXR - diffuse interstitial infiltrates
• HRCT scan - GGO
• Other - nodular infiltrates, hilar / mediastinal adenopathy & pleural effusion
• Blood eosinophilia in nearly 40%
• BAL fluid → predominance of lymphocytes (T-suppressor cells)

• Diagnosis requires 3 major criteria:
  – Histopathology - hypersensitivity pneumonitis
  – Radiographic evidence of interstitial and/or alveolar infiltrates
  – Negative blood cultures & sputum cultures

• 3 of 5 minor criteria:
  – Dyspnea of 8 weeks in duration
  – Nonproductive cough
  – RA O₂ saturation of ≤ 90%
  – Dlco of ≤ 70% of predicted
  – Leukocyte count of ≤ 15,000 cells/L
• Risk factors for toxicity include:
  – Symptoms within first 32 weeks of therapy
  – Multidrug regimens (synergy with cyclophosphamide)
  – Age > 50 yr / DM
  – Rheumatoid pleuro-pulmonary disease
  – Hypoalbuminemia


• No affect of dose, frequency, smoking status, previous lung disease & route on adverse effect
• PFT – not helpful in identifying at risk pt on low dose
• Chronic fibrosis develops ~ 7% of hypersensitivity reactions
• 8% die of progressive respiratory failure
Mitomycin

- Incidence ~ 5% (3 to 39%)
- Radiographic / physiologic changes similar to bleomycin
- Most frequently after 3\textsuperscript{rd} cycle
- Serial monitoring of DLco to detect clinically occult disease unproven but generally recommended
- Prednisone rapidly resolve symptoms / interstitial infiltrate
- Rarely induce microangiopathic hemolytic anemia concurrently with NCPE & renal failure which has mortality rate of 90\%
Retinoic Acid

- ATRA highly effective biological response modifier used to induces CR in acute promyelocytic leukemia
- Retinoic acid syndrome → ARDS-like seen in ~ 25% pt

- Sudden onset of fever, dyspnea, pleural / pericardial effusion, diffuse alveolar infiltrates & HRF
- Prednisolone (75 mg/d) reduces incidence ~ 8%

- Before steroid > 50 % patients required mechanical ventilation & mortality rate was 33%

Leukemia 1995; 9:774–778
Chemotherapeutic Agents/Newer Antineoplastic Drugs

• **Chlorambucil** $\rightarrow$ Tt of lymphoproliferative disorders has relatively rare toxicity – chronic pneumonitis / fibrosis

• **Cytosine arabinoside** $\rightarrow$ acute leukemia causes NCPE in 13 to 20% of patients

• Mortality rate 2 to 50% with reports of improve outcome with CS

• **Fludarabine** $\rightarrow$ cause chronic pneumonitis/fibrosis / hypersensitivity-type reaction which respond to CS

Chest 2002; 122:785–790
• **Gemcitabine** → Mx of solid tumors can induce potentially fatal ARDS
  • Toxicity ranges from 1 to 1.4% & includes
    – ARDS, NSIP, PF & PE

• **Taxanes** → induces bronchospasm & T1 hypersensitivity reaction in 30%
  • HP, NSIP, PF ARDS & PE

• **Topoisomerase I inhibitors** (irinotecan / topotecan) → NSIP and bronchiolitis obliterans
  • Synergy between irinotecan and paclitaxel or radiation ↑ frequency of pulmonary toxicity from 1.8 → 13% or 56%, respectively

Chest 2008; 133:528–538
**gefitinib** and **imatinib**

- pulmonary toxicity in ~ 2% consisting of NSIP, HP, PF, COP, alveolar hemorrhage, ARDS, & PE

- GM-CSF & G-CSF can cause a HP when administered in conjunction with other cytotoxic agents

- G-CSF – induce ARDS in presence of cytotoxic drugs
Nonchemotherapy-Associated Pulmonary Toxicity

Antiinflammatory Drugs

• Aspirin-bronchospasm and noncardiogenic pulmonary edema

• Aspirin-induced asthma occurs in 1% of healthy individuals and in up to 20% of asthmatic individual

• Symptoms of AIA occur within minutes to hours after ingestion and may be associated with facial flushing, rhinorrhea, angioedema, and conjunctivitis
• **Penicillamine**: antiinflammatory, antifibrotic, & copper-chelating agent → RA, scleroderma, primary biliary cirrhosis, and Wilson disease

• Pulmonary toxicity include
  – interstitial pneumonitis/fibrosis
  – bronchiolitis obliterans ± organizing pneumonia
  – drug-induced SLE
  – alveolar hemorrhage due to a pulmonary-renal syndrome
• Incidence- < 1% with subacute onset of dyspnea, cough, & wheez
• CXR - hyperinflation in the absence of infiltrates
• PFT- ↑ lung volumes & airflow limitation without BDR
• Lung biopsy → bronchiolar constriction caused by mononuclear inflammation & fibrosis

• Mx → drug withdrawal, supportive therapy, & consideration of a trial of corticosteroids, azathioprine, or cyclophosphamide
• Prognosis → bronchiolitis obliterans is poor with 50% mortality
• **Etanercept, Infliximab & Adalimumab** → used to block effects of TNF- in autoimmune diseases

• Reactivation of tuberculosis / fungal infections

• Recommended: screening & treatment for latent tuberculosis before use of drug

• **Etanercept / Infliximab** → NSIP, PF, loosely formed granulomatous inflammation, PE, ↑ size of RA nodules & SLE-like reactions

  Respir Med 2009; 103:661–669
Antimicrobial Drugs

• Nitrofurantoin
  – acute hypersensitivity-type reaction
  – chronic pneumonitis/fibrosis that mimics IPF

• Acute toxicity is a very rare (0.1%) seen with in 1 month of the first dose in 86% of patients

• Symptoms consist of dyspnea, cough, fever, chest pain, and a macular/papular skin rash

• Elevated ESR & peripheral blood eosinophilia

Eur J Respir Dis 1981; 62:180–189
• CXR
  – mixed alveolar/ interstitial infiltrative pattern
  – normal in 18% of patients
  – 1/3 have a small pleural effusion
• PFT - Restrictive pattern with reduced Dlco
• Prognosis \(\rightarrow\) favorable with drug withdrawal and therapy with corticosteroids
• ARDS seen in few with overall mortality rate 1\%
Cardiovascular Drugs

- **Amiodarone** → ventricular and SV arrhythmias refractory to other drugs
- Iodine - containing phospholipase inhibitor that causes lipid accumulation in nearly all tissues - lungs, skin, & liver

- Adverse pulmonary effects → 5 to 10% with high daily dose (400 mg/d) & prolonged duration (12 months)
- Large volume of distribution & long half-life of 30 to 60 days

- Lipid blockade → accumulation of undigested surfactant phospholipids in lung seen in virtually all patients
• **Histological features**
  – accumulation of foamy macrophages with characteristic lamellated inclusions in interstitium / alveolar spaces
  – hyperplasia of alveolar type II cells
  – widening of the alveolar septa with infiltration of lymphocytes, plasma cells, eosinophils, and neutrophils

• **Pulmonary toxicity manifest as**
  – interstitial pneumonitis/fibrosis, ARDS, COP,
  – mass lesions that can cavitate
  – EP, DAH and PE

• **Uncommon reactions include HP, alveolar hypoventilation, and bronchospasm**
• Risk factors
  – maintenance dose of 400 mg/d
  – age > 60 years
  – duration 6 to 12 months
  – angiography/acute lung injury
  – Cardio-thoracic surgery/ARDS

• Total cumulative dose or serum levels are not useful

• ↓ in Dlco & ↑ gallium uptake are supportive but not reliable predictors of toxicity in absence of clinical / radiographic abnormalities
• Diagnosis is one of exclusion
• Chest CT scans $\rightarrow$ high-attenuation areas caused by the iodine
• KL-6 glycoprotein secreted by alveolar type II cells is useful serum marker $\rightarrow$ increased (> 500 U/mL) in ILD caused by IPF, radiation, amiodarone
• sensitivity and specificity of an increased serum KL-6 level is 94% and 96%, respectively

Am J Respir Crit Care Med 2002; 165:378–381
• Mx→ withdrawal & new antiarrhythmic agent / implantation of an automatic cardioverter/defibrillator

• CS trial in symptomatic patients but efficacy not established

• Radiographic resolution in about 2 months & Tt to continue at least 6 months to reduce likelihood of relapse

• Recurrent can occur & if amiodarone is only effective agent – dose must be reduced to the minimum & CS to be added
Illicit Drugs

Causes wide array of pulmonary disorders
• Alveolar hypoventilation (hypercarbic respiratory failure)
• Aspiration
• Noncardiogenic pulmonary edema
• Barotrauma
• Endocarditis/septic emboli
• Foreign-body granulomatosis
• PIE
• COP
• Alveolar hemorrhage
• Bronchospasm
• Interstitial pneumonitis/fibrosis
• HIV associated infection.
• NCPE complication of **heroin, cocaine, methadone & Naloxone**

• Pathogenesis not clear but proposed
  – Altered alveolar/capillary permeability
  – Neurogenic pulmonary edema
  – Direct opiate cytotoxicity
  – Drug hypersensitivity
  – Hypoxemic alveolar injury

• Mx - supportive care including MV \(\rightarrow\) needed in 40%
• Prognosis good with resolution of PE in 48 to 72 h
Radiation

- Thoracic irradiation causes dose-related reversible changes characterized by dry cough & pathologic changes of bizarre type II cells, hyaline membranes, edema, & fibrosis

- Patients who receive therapy for lung or breast carcinoma, Hodgkin’s disease or NHL, or total body irradiation before bone marrow or peripheral stem cell transplantation

- Expression of radiation injury to lung depends upon direction of radiation beam
• Induce changes in areas remote from radiation beam as suggested by
  – ↑ BAL lymphocytes or gallium uptake in both irradiated & non-irradiated lung
  – Organizing or eosinophilic pneumonia following breast radiation therapy may involve nonirradiated areas
  – Acute severe radiation pneumonitis and ARDS outside irradiated lung

• Concomitantly affect pleura, myocardium, heart valves, pericardium, pulmonary veins, mediastinum, lymphatic channels, & phrenic nerves
• The risk of radiation pneumonitis depends on
  – individual susceptibility of host
  – Delivered dose to lung
  – Daily / fractionation schedule
  – Treatment with chemotherapeutic agents or oxygen
• Other factors include older age and a low baseline lung function or PaO₂
• Recent pneumonectomy is a potential risk factor because
  – pulmonary reserve is compromised
  – remaining lung can be exposed to radiation as post-pneumonectomy hemithorax contracts

Ongoing smoking may have a protective effect
### Toxicity Criteria for Pneumonitis

<table>
<thead>
<tr>
<th>Scoring System</th>
<th>CTCAE</th>
<th>RTOG/EORTC (LENT-SOMA)</th>
<th>SWOG (33)</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Asymptomatic;</td>
<td>Asymptomatic or mild symptoms (dry cough), with radiographic findings</td>
<td>Asymptomatic or symptoms not requiring steroids with radiographic findings</td>
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<td></td>
<td>radiographic findings only</td>
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<td>Moderately symptomatic (severe cough fever)</td>
<td>Initiation of or increase in steroids required</td>
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<td>interfering with ADL</td>
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<td></td>
<td>Symptomatic;</td>
<td>Severe respiratory insufficiency; continuous oxygen/assisted ventilation</td>
<td>O₂ required</td>
</tr>
<tr>
<td></td>
<td>interfering with ADL; O₂ indicated</td>
<td></td>
<td>Assisted ventilation necessary</td>
</tr>
<tr>
<td></td>
<td>Life-threatening</td>
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<tr>
<td></td>
<td>ventilatory support</td>
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<td></td>
<td>indicated</td>
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<td>Death</td>
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<td>Death</td>
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**Notes:** Abbreviations: CTCAE = Common Terminology Criteria for Adverse Events; ADL = activities of daily living; RTOG = Radiation Therapy Oncology Group; EORTC = European Organization for the Research and Treatment of Cancer; LENT-SOMA = Late Effects on Normal Tissue-Subjective, Objective, Management and Analytic Scales; SWOG = Southwest Oncology Group.

• Patterns of radiation pneumonitis
  – Classic / sporadic radiation pneumonitis
• Approximately 10% of patients develop radiographic changes consistent with radiation pneumonitis
• Symptoms include a dry cough, moderate fever, and dyspnea
• On imaging, changes typically develop 1 to 2 months → discrete haze, ill-defined patchy nodules or an area of condensation
• Mild restrictive lung function can develop early in the course of radiation pneumonitis

• lung volumes normalize in 18 to 24 months
• lung biopsy is rarely needed to establish the diagnosis
• Histologic features
  – Interstitial edema, hemorrhage, and a fibrinous exudate in early stage
  – Distortion, fibrosis, and type 2 pneumocyte dysplasia in late stage

• Patients respond well to the administration of corticosteroids

• Late complications of chronic radiation pneumonitis
  – bronchiectasis in the fibrotic area
  – Pneumothorax
  – colonization by Aspergillus spp.
  – radiation-induced myocardial or valvular injury
Summary

• Different drugs can cause similar pulmonary syndromes and presentations
• Most common presentations are an abnormality on the chest radiograph and a symptom complex
• Early diagnosis is very important and requires the physician to be vigilant for problems in the appropriate clinical settings
• The diagnosis is usually one of exclusion
• Stopping the drug is sufficient therapy for most drug toxicities
• Corticosteroid administration may also be needed
THANKS