Other Airway Conditions Involving the Distal Airway (Bronchiolitis)
State-of-the-Art
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Learning Objectives

• Recognize naming and types of bronchiolitis and common causes
• Explain factors involved with diagnosing and treating bronchiolitis and similar airway conditions
• Recall key pathologic and radiographic features of various distal airway conditions
Peripheral airways
• Defined as airways with less than 2 mm in diameter and no cartilage

Membranous bronchioles
• Have full fibromuscular wall but this wall is very thin
Peripheral airway (<2 mm diameter)

Cellular infiltrates
- Intraluminal
  - Respiratory bronchiolitis
- Mural
  - Diffuse panbronchiolitis
- Peribronchial/Interstitial
- Bronchiolitis Obliterans
- Peribronchial
  - Respiratory bronchiolitis with fibrosis
  - ILD with small airway component
  - HP
  - CTD-ILD

Lymphoid aggregates
- Follicular Bronchiolitis
  - CTD
  - Irritant
  - Cigarette smoking

Lymphocyte
- Chronic/Cellular Bronchiolitis
  - CTD
  - Infection
    - Viral: (RSV, rhinovirus, influenza, adenovirus, metapneumovirus, parainfluenza, coronavirus, bocavirus)
    - Mycoplasma
    - Legionella
    - Drug

Proliferative (luminal polyps)
- NO₂ gas inhalation

Constrictive (mural scarring)
- Transplant rejection
- Lung and heart-lung
- GVHD
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  - Scleroderma
  - SJögren syndrome
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  - NO₂
  - Diacetyl
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  - Mustard gas
- Drug
  - Penicillamine
  - Aspiration
  - Idiopathic
- Misc: Ulcerative colitis, Steven’s-Johnson, neuroendocrine cell hyperplasia ± carcinoid tumorlets, Saurops androgynus ingestion
<table>
<thead>
<tr>
<th></th>
<th>Chronic Bronchitis</th>
<th>Bronchiectasis</th>
<th>Asthma</th>
<th>Emphysema</th>
<th>Bronchiolitis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Anatomic site</strong></td>
<td>Bronchus</td>
<td>Bronchus</td>
<td>Bronchus</td>
<td>Acinus</td>
<td>Bronchiole</td>
</tr>
<tr>
<td><strong>Pathology</strong></td>
<td>Mucous gland</td>
<td>Airway dilatation, hyperplasia, hypersecretion</td>
<td>Smooth muscle hyperplasia, excess mucus, inflammation</td>
<td>Airspace enlargement, wall destruction</td>
<td>Inflammatory scarring, obliteration</td>
</tr>
<tr>
<td><strong>Etiology</strong></td>
<td>Tobacco smoke, air pollutants</td>
<td>Persistent or severe infections</td>
<td>Immunologic or undefined causes</td>
<td>Tobacco smoke</td>
<td>Tobacco smoke, air pollutants, miscellaneous</td>
</tr>
<tr>
<td><strong>Main symptoms</strong></td>
<td>Cough, sputum production</td>
<td>Cough, purulent sputum, fever</td>
<td>Episodic wheezing, cough, dyspnea</td>
<td>Dyspnea</td>
<td>Cough, dyspnea</td>
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Assessment and treatment of acute toxic inhalations

Clayton T. Cowil

Purpose of review
Acute toxic inhalation exposures affect thousands of individuals worldwide each year. The acute evaluation of these inhalated exposures is often fraught with difficulty in identifying a specific agent, may involve multiple compounds, and a wide variety of responses are seen depending on the physical properties of the specific toxicant, the length of time of inhalation, and the concentration of the exposure. Recognizing key aspects of the most common acute toxic inhalations is useful in developing a diagnosis and treatment strategy.

Recent findings
Use of sequential observations with flexible bronchoscopy has been the standard of care for assessing airway injury, and virtual bronchoscopy using computed tomographic images in a three-dimensional reconstructed image can now better identify airway narrowing. Use of [18F]fluorodeoxyglucose uptake, as measured by PET, has the potential for early recognition of delayed acute lung injury in toxic inhalation exposures. Development of a standardized respiratory injury grading system is ongoing with a recent multicenter trial nearly complete, allowing for more accurate estimates of eventual outcomes and guide levels of intensity of care for patients with acute inhalation injury. Removal from the source of exposure and airway support remain the first critical aspect of treatment, and additional therapies have been studied recently that focus on altering molecular mechanisms of acute cellular injury, expanding potential treatments beyond other pharmacotherapeutic strategies utilized previously such as mucolytics, bronchodilators, and inhaled anticoagulants.

Summary
Although a prevalent source of airway injury, exposure to acute toxic inhalants is often difficult to assess and prognosticate, and challenging to treat.

Keywords
acute inhalation injury, acute toxic inhalants, gasorous inhalation, inhaled irritants, toxic inhalations
Which of the following statements regarding bronchiolitis is MOST CORRECT?

A. Toxic inhalations make up the majority of cases of bronchiolitis.
B. Bronchiolitis causes symptoms in all individuals with the condition.
C. Lupus and rheumatoid arthritis have been associated with causing bronchiolitis.
D. Finding small airways changes on the FEF25-75 of spirometry is pathognomonic for bronchiolitis.
E. Azithromycin has been used in bronchiolitis for its anti-microbial rather than its anti-inflammatory effects on the small airways.
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Bronchiolitis obliterans (also known as obliterative bronchiolitis or constrictive bronchiolitis)

- Common symptoms include dyspnea and cough;
- PFTs normal or show airflow limitation without bronchodilator reversibility;
- Has predisposing process (e.g., inhalational or drug exposure, rheumatic disease, lung or hematopoietic transplant);
- Expiratory air trapping (mosaic or diffuse) and bronchial wall thickening (e.g., "v" or "y" shaped branching linear opacities),
- Centrilobular nodules
Constrictive bronchiolitis (BO)

- Airway disease that surrounds the lumen with fibrotic concentric narrowing and obliteration.
- Mosaic pattern seen on the expiratory high-resolution chest CT scan is diagnostic in an individual with shortness of breath, early inspiratory crackles, and irreversible airflow obstruction.
- Swyer-James-MacLeod syndrome is no longer considered a congenital disorder but as constrictive bronchiolitis detected in young adults who had infectious pneumonia during infancy.
- Azithromycin may be effective in some lung transplant recipients for treatment of bronchiolitis obliterans syndrome for prevention of constrictive bronchiolitis.
Optimal treatment unknown:

- Stop exposure to potential inciting agents
- Symptomatic treatment with inhaled bronchodilators and oxygen;
- Other options: macrolides, glucocorticoids, immunosuppressive agents, anti-reflux therapy, lung transplantation
What findings are noted in this CT image seen commonly in constrictive bronchiolitis?

- Pulmonary nodules
- Tram track lines
- Mosaic attenuation
- Vascular injection
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Airway-centered interstitial fibrosis

- Associated with chronic nonproductive cough;
- Usually seen in smokers;
- PFTs restrictive or obstructive;
- Percentage of lymphocytes on bronchoalveolar lavage is less than 40%;
- See peribronchovascular ground glass opacities, traction bronchiectasis, and thickening of bronchial walls;
- Centrilobular and bronchiolocentric inflammatory infiltrate with peribronchiolar fibrosis and an absence of granulomas;
- Treat with systemic or inhaled glucocorticoids
Which of the following pathogens is most commonly associated with the development of bronchiolitis in children?

A. Respiratory syncytial virus (RSV)
B. Noravirus
C. Strongyloides
D. Streptococcus pneumoniae
E. Cladosporidium
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Acute Bronchiolitis

• Seen most commonly as a result of viral infectious diseases in the first two years of life

• 2-3% of children in the first 12 months of life are hospitalized with bronchiolitis, resulting in 125,000 hospitalizations and 200 to 500 deaths each year in the United States alone

• CDC data show the prevalence of bronchiolitis more than doubled between 1980 and 1996
Peripheral airway (<2 mm diameter)

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Fibrotic/Fibroplastic
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  - Idiopathic
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Proliferative bronchiolitis

• Distinctive histopathological pattern in which characteristic intraluminal fibrotic buds, called Masson bodies, extend beyond alveolar ducts to alveoli

• When proliferative bronchiolitis is associated with extension of inflammatory cells into the more distal pulmonary parenchyma, the process is called organizing pneumonia

• It is not uncommon to identify foamy macrophages in the alveolar spaces

• Associated with NO$_2$ inhalations
Proliferative bronchiolitis

• Usually seen in the context of cryptogenic or secondary organizing pneumonia or nitrogen dioxide (NO₂) exposure
• Diffuse or patchy ground glass or consolidative opacities
• Fibroblast proliferation and an organizing, polypoid intraluminal exudate in respiratory bronchioles and alveolar ducts
• Stop any inciting exposure
• Start systemic glucocorticoid trial
Follicular bronchiolitis (mural)

- Characterized by progressive dyspnea
- Associated with rheumatic diseases, immunodeficiency, hypersensitivity pneumonitis
- Centrilobular nodules; may have patchy ground glass opacity
- Polyclonal hyperplasia of bronchiolar associated lymphoid tissue (BALT) produced by antigen stimulation (lymphoid aggregates), with reactive germinal centers distributed along the bronchioles and less frequently more proximal to the bronchi
- Treat underlying disease
Respiratory bronchiolitis (intraluminal)

- Almost exclusively in smokers
- Often seen as asymptomatic finding on biopsy performed for another reason
- Diffuse or patchy ground glass opacities or fine centrilobular nodules and air trapping; bronchial wall thickening
- Mild bronchiolar inflammation, tan-pigmented macrophages within the lumens of first and second order respiratory bronchioles
- Treatment is cigarette smoking cessation
Respiratory bronchiolitis

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Diffuse panbronchiolitis

- History of sinusitis (75%) and productive cough;
- Generally limited to patients in Japan or other areas in SE Asia
- Diffuse centrilobular opacities, nodular and linear (tree-in-bud) opacities, thickened and dilated bronchiolar walls, and large cystic opacities with dilated proximal bronchi (in advanced disease)
- Bronchiolar transmural infiltrate composed of lymphocytes, plasma cells, and distinctive lipid-laden "foamy" macrophages
- Diagnose through compatible clinical findings in a patient in Japan; otherwise lung biopsy
- Macrolide antibiotic for six months or longer
Summary

• Bronchiolitis is one category of conditions affecting the distal airways -- with acute forms associated with viral infections in infants (RSV)

• Nomenclature was modified to describe pathological features (cellular v. fibrotic -- proliferative v. constrictive bronchiolitis)

• May be a continuum of airway inflammation that is similar in other inflammatory airway conditions causing asthma and COPD

• Toxic inhalations in addition to connective tissue diseases and infections are etiologies to consider in adult bronchiolitis
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