CME

# A review of organizing pneumonia

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## ABSTRACT

Organizing pneumonia is a clinical and pathological syndrome that describes a lung injury caused by an inflammatory reaction in the alveolar connective tissue. Classified as an interstitial lung disease, it can be secondary to infection, drug toxicity, connective tissue disorders, inhalation injuries (cocaine), organ transplant, or radiotherapy, and also can be idiopathic. Although organizing pneumonia is not a new phenomenon, it has been noted to be a complication of COVID-19, and should be considered in patients who have had COVID-19 and have atypical chest imaging, because treatment includes corticosteroids instead of antimicrobials.


**Keywords:** pneumonia, organizing, COVID-19, chest radiograph, respiratory, BOOP

## Learning objectives

- Define organizing pneumonia and identify potential causes.
- Describe radiographic findings for diagnosis of organizing pneumonia.
- Identify the incidence of organizing pneumonia after COVID-19.
- Describe the treatment course for patients with organizing pneumonia.



The changing designations of organizing pneumonia may be confusing. Historically known as *bronchiolitis obliterans organizing pneumonia* (BOOP), organizing pneumonia is not associated with the rare chronic disease bronchiolitis obliterans. Bronchiolitis obliterans describes irreversible damage of the small airways caused by inhalation injuries, infections or as a complication of stem-cell and lung transplants.[1] The term BOOP was first mentioned by Geddes and colleagues in 1977, and the name persisted partly because BOOP is fun to pronounce.[2] Unlike bronchiolitis obliterans, organizing pneumonia is reversible with corticosteroids. The term *cryptogenic organizing pneumonia* (COP) was coined in 1983 by Davidson and colleagues to describe organizing pneumonia without known cause.[3] In 2002, the American Thoracic Society and European Respiratory Society adopted COP in place of BOOP.[4] The American Thoracic Society classifies COP as an interstitial pneumonia because an infiltrative imaging pattern can be seen and the interstitium may be involved when examining the pathologic specimen.[5] This classification again causes confusion, because organizing pneumonia is an intra-alveolar pattern, not primarily an interstitial injury.

## BRONCHIOLAR DISORDERS IN ADULTS

When the alveolar epithelium is damaged, the basal lamina is interrupted and coagulative proteins flow into the alveolar airspace; fibrin is then deposited as a part of the coagulation cascade. Fibroblasts and myofibroblasts then form a connective tissue matrix that has an appearance like intra-alveolar buds.[6,7] The buds of granulation tissue are called *Masson bodies*. This process is similar to skin wound healing.[8] If inflammation involves the lung parenchyma, consider alternative diagnoses, including nonspecific interstitial pneumonia, usual interstitial pneumonia, and idiopathic pulmonary fibrosis.[9]

**Causes** Organizing pneumonia occurs after a wide range of insults. Causes may be infectious (including bacteria, viruses, parasites, and fungi), related to drug toxicity, or inflammatory/autoimmune (**Tables 1** and **2**). When a cause is not identified, organizing pneumonia is classified as COP. Although COP is defined as being idiopathic, researchers suspect that in most patients with COP, the primary cause was just not identifiable.[10]

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DOI:10.1097/01.JAA.0000918776.59717.eb

## Key points

- Organizing pneumonia, historically known as BOOP, is a reactive intra-alveolar lung injury.
- Presentation is subacute; patients typically have several weeks of malaise and cough.
- Lower lobe consolidation, ground-glass opacities, and crazy paving can be seen on chest radiograph.
- Corticosteroids are the mainstay of treatment.

**Incidence and prevalence** Estimating the incidence of organizing pneumonia is challenging, because it arises secondarily from a number of insults; however, several studies indicate that the prevalence may be higher than expected.[11-14] A 20-year retrospective postmortem analysis of patients in Iceland found that 2 patients per 100,000 met the diagnostic criteria for COP versus secondary organizing pneumonia.[11] Two registry studies of interstitial lung disease reported the prevalence of COP between 5% and 10%.[15] In a postmortem series of SARS-CoV-positive patients in Toronto in 2003, one-quarter of patients examined had organizing pneumonia or acute fibrinous and organizing pneumonia.[12] Although the body of knowledge about COVID-19 is still growing, a comprehensive literature review found that 22% of COVID-19 patients also had acute fibrinous and organizing pneumonia, with epithelial patterns of damage noted in all stages of the viral illness but with a fibrotic pattern appearing about 3 weeks after the acute illness.[13] In a multicenter study conducted by Jin and colleagues, 54.5% of patients with COVID-19 had a preliminary diagnosis of organizing pneumonia.[14] No precise data exist for the incidence of COP, but it is thought to be 1 to 3 per 100,000 hospital admissions. COP classically develops in patients in their 40s and 50s and equally affects both sexes.[9] Organizing pneumonia is not associated with smoking, nor have any other predisposing factors been identified.[16]

**Presentation and diagnosis** The clinical course of patients with organizing pneumonia is nonspecific and subacute. Typically, patients present with a prodrome of malaise, cough, and dyspnea that can last for several weeks.[17] Hemoptysis, chest pain, night sweats, and arthralgia are uncommon.[16] Patients frequently have been treated for presumed bacterial pneumonia but empiric antibiotics have no effect.[9] The physical examination may reveal hypoxemia, crackles, and bronchial breath sounds on lung auscultation.[17,18] Connective tissue diseases and toxicities may cause organizing pneumonia; therefore, when taking the patient's history, assess for connective tissue disease, medications, and exposure history.[9]

Laboratory analysis should include complete blood cell (CBC) count, erythrocyte sedimentation rate (ESR), and C-reactive protein (CRP), because leukocytosis with neutrophilia and elevated inflammatory markers can be present in patients with COP.[9] Pulmonary function tests may show a restrictive pattern with reduction in diffusion of lung capacity for carbon monoxide. On chest radiograph, 60% to 90% of patients with organizing pneumonia have focal or multifocal consolidation, with or without air bronchograms.[6] Consolidation can appear in all lung zones but most commonly is noted in the peripheral and lower lung. Bronchocentric forms of organizing pneumonia occur in one-third of patients and are associated with nodular organizing pneumonia and patchy ground-glass opacities.[6] A third pattern to note is called *crazy-paving*, and is characterized by patchy ground-glass opacities with interlobar septal thickening on CT imaging. This pattern has been associated with secondary organizing pneumonia from drug toxicities, specifically nitrofurantoin and bleomycin.[13] Pleural effusions are uncommon but have been present in some case studies.[19]

**TABLE 1.** Infectious causes of organizing pneumonia[16,18,19,21,26]

| | |
|---|---|
| **Bacterial** | *Burkholderia cepacia, Chlamydia pneumoniae, Coxiella burnetii, Legionella* pneumonia, *Mycobacterium abscessus, Mycoplasma pneumoniae, Nocardia asteroides, Pseudomonas aeruginosa, Serratia marcescens, Staphylococcus aureus, Streptococcus* group B, *Streptococcus pneumoniae* |
| **Viral** | Adenovirus, COVID-19, cytomegalovirus, human herpesvirus 7, HIV, influenza (A and B), parainfluenza, respiratory syncytial virus |
| **Fungal** | *Cryptococcus neoformans, Penicillium janthinellum, Pneumocystis jirovecii* |
| **Parasitical** | *Plasmodium vivax, Dirofilaria immitis* |

**TABLE 2.** Noninfectious causes of organizing pneumonia[20,22,26-29]

| | |
|---|---|
| **Drug toxicities** | 5-aminosalicylic acid, amiodarone, amphotericin B, bleomycin, bisulfan and cyclophosphamide, carbamazepine, cephalosporin, cocaine (inhaled), dasatinib, doxorubicin, gold salts, interferon alpha and alpha 2b, interferon plus ribavirin, interferon beta1alpha, L-tryptophan, meslazine, methotrexate, minocycline, nitrofurantoin, phenytoin, sirolimus, sotalol, sulfasalazine, tacrolimus, ticlopidine, trastuzumab, vancomycin, vinbarbital-aprobarbital |
| **Inflammatory/autoimmune** | Allogenic hematopoietic stem cell transplant, anti-JO-1 auto antibodies, CREST syndrome (calcinosis, Raynaud phenomenon, esophageal dysmotility, sclerodactyly, telangiectasia), dermatomyositis-polymyositis, lung transplant, primary biliary cirrhosis, rheumatoid arthritis, scleroderma, Sjögren syndrome, systemic lupus erythematosus |

Organizing pneumonia is a diagnosis of exclusion; therefore, bronchoscopy and bronchoalveolar lavage (BAL) are indicated to rule out infection, malignancy, or other inflammatory disorder. The differential white cell count from the BAL may show a mixed picture in patients with COP, with increased lymphocytes, neutrophils, and eosinophils, and decreased lymphocyte CD4/CD8 counts.[16]

Diagnosing organizing pneumonia can be challenging, in part because of the terminology behind the process. If pathology of lung biopsy mentions Masson bodies, consider whether the disease process is primary or secondary, and consider a broad differential. However, if a chest radiograph demonstrates an evolving multifocal consolidation when acute infection is not on the differential, organizing pneumonia should be at the top of the differential. Ultimately, the diagnosis often requires the expertise of an interdisciplinary team including radiology, pathology, and pulmonology.[10]

## TREATMENT

Corticosteroids are the standard of treatment and should be considered promptly for patients with severe organizing pneumonia, because treatment delay can be fatal.[5] Often, the response is dramatic, with clinical improvement in 48 hours and complete resolution of radiographic infiltrates in several weeks.[16] Recommended dosing is variable: in the 1990s, prednisone 1 to 1.5 mg/kg/day for 1 to 3 months was common. However, some researchers recommend prednisone 0.75 mg/kg/day.[16] A case report of a patient with acute fibrinous organizing pneumonia related to Sjögren syndrome describes treating the patient with 80 mg IV methylprednisolone for 1 week; the patient was discharged on prednisone 40 mg daily for 1 week with a 5-mg reduction every week thereafter.[20] Dosing for secondary organizing pneumonia after an infection also is not standard. In a case study of a patient who had secondary organizing pneumonia after *Mycobacterium abscessus* lung disease, the patient was successfully treated with oral prednisone 30 mg, which was gradually tapered over 6 months.[21] When organizing pneumonia is secondary to drug toxicity, the offending medication should be discontinued, and case reports indicate successful treatment with prednisone 30 mg daily for 4 weeks.[22] A proportion of patients have relapsed after corticosteroid reduction; therefore, if a low dose and shorter duration of treatment is chosen to avoid adverse reactions, relapse is possible.[5] Although single-center observational studies and case reports exist, consensus is lacking about corticosteroid dosing and duration for organizing pneumonia secondary to COVID-19. Therefore, a multicenter randomized clinical trial is needed.[23] Consider *Pneumocystis* pneumonia (PCP) prophylaxis for patients who are prescribed a glucocorticoid equivalent of prednisone 20 mg for 1 month or greater.[24] If the duration of corticosteroid treatment is expected to be greater than 3 months, consider calcium and vitamin D supplements to prevent glucocorticoid-induced osteoporosis.[25]

## PROGNOSIS

Although most patients with organizing pneumonia recover after corticosteroid treatment, some develop severe disease.[5] Patients with widespread opacities on chest imaging and hypoxemia meet the definition for acute respiratory distress syndrome (ARDS) and may need mechanical ventilation. In a small number of patients, death has been reported when treatment was delayed.[5]

## CONCLUSION

Although organizing pneumonia remains a diagnosis of exclusion, its increasing incidence and prevalence mean it should be considered in patients with abnormal chest radiographs who have not improved after antimicrobial therapy. Classically, presentation is subacute, and is secondary to a variety of lung injuries such as infections caused by viruses, bacteria, or drug toxicity. Although the diagnosis may be challenging and hinges on radiographic and histopathologic findings, once the acute infection has been ruled out, the offending agent should be removed if possible and patients started on corticosteroids. **JAAPA**

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