

# Bronchiolitis obliterans organizing pneumonia, 25 years: a variety of causes, but what are the treatment options?

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## Gary R Epler

*Pulmonary and Critical Care Medicine,  
Brigham and Women's Hospital,  
75 Francis Street, Boston,  
MA 02115, USA  
Tel.: +1 617 732 7621  
[gepler@partners.org](mailto:gepler@partners.org)*

Bronchiolitis obliterans organizing pneumonia is an inflammatory lung disease involving the distal bronchioles, respiratory bronchioles, bronchiolar ducts and alveoli. Its cause is generally unknown, but there are several known causes and associated systemic diseases. The clinical features include cough, shortness of breath and bilateral crackles. The vital capacity is slightly decreased, and the diffusing capacity is moderately to severely decreased. The high-resolution chest CT scan shows bilateral ground-glass opacities with air bronchograms and triangular, pleura-based opacities. Corticosteroid therapy is the best treatment option. The outcome of patients suffering from bronchiolitis obliterans organizing pneumonia is good, as up to 80% of individuals will be cured.

**KEYWORDS:** amiodarone BOOP • bird feather down BOOP • bronchiolitis obliterans organizing pneumonia • cryptogenic organizing pneumonia • Epler's pneumonia • macrolide treatment • organizing pneumonia • radiation BOOP

There are many types and causes of bronchiolitis obliterans organizing pneumonia (BOOP). The treatment is often similar, but utilizing information regarding BOOP gathered from the last 25 years has created important distinctions that need to be considered for optimal patient care. BOOP is defined as organized polypoid granulation tissue in the distal airways extending into the alveolar ducts and alveoli [1,2]. It is an inflammatory disorder involving both the peripheral bronchioles and alveoli simultaneously and has distinctive radiographic findings, histologic features and response to therapy. The general term, organizing pneumonia (OP) mainly involves the respiratory bronchioles, alveolar ducts and alveoli, and can be subcategorized into either cryptogenic OP or secondary OP. These two conditions have been described elsewhere [3,4]. The term BOOP is used here because it continues to be recognized and used throughout the world [5–7]. It is a specific pulmonary lesion recognized by pathologists with a characteristic clinical pattern. The term BOOP is preferred for the nonidiopathic types, such

as drug-related BOOP, systemic disease-related BOOP, radiation therapy-related BOOP, occupational and environmentally-related BOOP, and newly described types. For patients, BOOP is easy to remember and the term is used to advance their understanding of the disease by obtaining accessible scientific publications.

This diffuse parenchymal lung disease has the following histological criteria:

- Organized polypoid granulation inflammatory tissue in the distal bronchiole airways, respiratory bronchioles, alveolar ducts and alveoli;
- Absence of extensive interstitial fibrosis;
- Absence of traction bronchiectasis;
- Absence of histological honeycombing [1,2].

Crackles are heard on examination and the high-resolution chest CT scans show triangular-shaped ground-glass opacities with air bronchograms. There are several types of BOOP, some with no known cause, others from specific causes, and some associated with systemic disease.

### Box 1. Bronchiolitis obliterans organizing pneumonia with no known cause.

- Idiopathic BOOP
- Rapidly progressive BOOP
- Focal nodular BOOP

BOOP: Bronchiolitis obliterans organizing pneumonia.

#### BOOP with no known cause

Idiopathic BOOP is the most common form and continues to be reported throughout the world [5–7]. Box 1 illustrates the three types of BOOP with no known cause. The annual incidence of OP in Iceland was 1.97 out of 100,000, and 1.1 out of 100,000 for primary OP [8]. Men and women are affected equally [7]. The average age is 50 years of age with a range from 12 to 93 years [5–7]. Symptoms include cough and shortness of breath in 50–70% of patients [5–7], and flu-like illness with fever in up to 50% [7]. Wheezing and hemoptysis are unusual. There are bilateral end-inspiratory crackles in up to 80% of patients [5], although in some individuals there may be quite extensive radiographic findings with no crackles. There is no relationship to smoking. Laboratory studies show increased sedimentation in most patients and increased leukocyte count in one-third of patients [6]. The bronchoalveolar lavage may show a high percentage of lymphocytes, more than 25% in 72% of individuals [7]. Pulmonary function shows a decrease in vital capacity in 60% and the diffusion capacity is abnormal in most patients who have symptoms and typical bilateral patchy infiltrates [6]. There is no airflow obstruction. The chest x-ray shows bilateral patchy infiltrates. The high-resolution chest CT scan shows bilateral ground-glass opacities with air bronchograms and often triangular shape with the base of the triangle along the pleural surface. Half of the infiltrates are in the upper lungs and half in the lower lungs, migration of infiltrates occur in some patients, effusions and cavities are rare, and honeycombing is not seen [5–7].

Rapidly progressive BOOP is a rare form of the idiopathic type with an acute onset of several days leading to respiratory failure and requirement for mechanical ventilation [6,9,10]. A flu-like illness may occur early on, and this type can occur in individuals with lupus erythematosus or rheumatoid arthritis [6]. Acute respiratory failure develops rapidly with severe hypoxemia. The chest x-ray shows a white-out of both lungs, and the chest CT scan shows ground-glass opacities and alveolar consolidation. This type of BOOP has the same appearance as acute interstitial pneumonia and diffuse alveolar damage and the fulminant type of acute fibrinous OP [11], except the chest CT scan for BOOP shows no honeycombing or traction bronchiectasis, and the pathology shows no hyaline membrane reaction [9].

Focal nodular BOOP shows a single rounded opacity, and has an excellent prognosis [7,12]. Among 26 patients with unifocal opacities, most were asymptomatic while some had cough, and the PET scan was positive in 100% of patients [12]. The process is often seen as an incidental finding in patients, without symptoms and normal pulmonary function tests, and the rounded lesion is removed as part of a diagnostic surgical procedure. There was no recurrence among the 26 patients [12]. In some situations, there may be multiple nodules.

#### BOOP from known causes

Box 2 illustrates the eight types of BOOP resulting from known causes. Post-respiratory infection BOOP occurs after an infectious pneumonia. Instead of restoration of the normal lung, an organized pattern of inflammation develops. BOOP diagnosis should be considered when patients develop patchy ground-glass opacities while being treated for lung infection, especially if they are transplant recipients or have a dysfunctional immune disorder [13–16]. This type usually occurs after viral pneumonias such as influenza, adenovirus or cytomegalovirus, or bacterial pneumonias such as *Chlamydia*, but it also occurs after *Legionella* pneumonia, malaria pneumonia, *Pneumocystis*, after fungal infections such as *Cryptococcus neoformans* [13], and from a hydatid cyst [15]. Death from some infection-related BOOP has been reported. A 68-year-old man underwent a stem cell transplant for acute myeloid leukemia and developed *Pneumocystis jirovecii* infection 2 months post-transplant [16]. The infection was treated, but he developed fever, cough, shortness of breath, and new rapidly progressive bilateral patchy ground-glass opacities. A lung biopsy at 4 months post-transplant showed BOOP. High-dose corticosteroids had been started before the biopsy; despite this the patient died 2 days later.

#### Drug-related BOOP

There are more than 35 medications that may cause BOOP [17]. These medications include antimicrobial agents such as minocycline, nitrofurantoin, cephalosporin and amphotericin-B. Nitrofurantoin BOOP continues to be reported as shown by a 71-year-old woman who had taken nitrofurantoin for 6 months prior to developing a nonproductive cough, fever, shortness of breath, bilateral crackles, patchy infiltrates and an effusion [18]. There was complete resolution of symptoms with prednisone therapy, which was discontinued after 16 months; however, the diffusion capacity remained abnormal at 53% predicted. There have been two case reports of daptomycin-related BOOP [19,20]. The first individual was an 84-year-old man who was treated with 4 weeks of intravenous daptomycin for an infected knee prosthesis. The chest CT scan showed bilateral peripheral ground-glass opacities, one of which was triangular [19]. The second individual was a 54-year-old man who developed shortness of breath 14 days after intravenous daptomycin treatment for a methicillin-resistant *Staphylococcus aureus* infection [20]. Abacavir is HIV nucleoside analogue reverse transcriptase inhibitor that appeared to cause BOOP after 2 weeks of treatment in a 52-year-old woman infected with HIV [21]. The abacavir was discontinued, and she showed a remarkable improvement with dramatic resolution of the bilateral infiltrates.

The anticancer agents causing BOOP include busulfan, methotrexate, bleomycin, doxorubicin, thalidomide, cytosine-arabinoside, cytarabine, ifosfate, chlorambucil, rituximab and oxaliplatin. Platinum-based chemotherapy may also cause BOOP [22,23]. A 30-year-old woman with rectal cancer and a single liver metastasis had a liver tumor resection and was given adjuvant therapy with 5-fluorouracil, leucovorin and oxaliplatin, and after 10 weeks and the sixth cycle, she developed a cough

and progressive shortness of breath [22]. A 47-year-old patient developed a BOOP following oxaliplatin treatment for metastatic rectal cancer [23]. Fludarabine, cytosine arabinoside and mitoxantrone-related BOOP has been reported in a 31-year-old man treated for acute myeloid leukemia [24].

Cardiovascular drugs implicated in the development of BOOP include amiodarone and acebutolol. Amiodarone-related BOOP is the most commonly reported drug-related reaction. Camus *et al.* reported the occurrence is from 1 to 15% [25]. Boroso *et al.* found six cases among 197 patients (3%) in a study in Spain [26]. Amiodarone and the metabolite desethyl-amiodarone are cationic amphiphilics that accumulate in tissues including the lungs. These compounds localize in cell lysosomes and block turnover of endogenous phospholipids, which explains the presence of foamy lipid-laden macrophages in lavage or lung tissue. Clearance of these substances from tissues is very slow as autopsy studies have shown significant amounts of both compounds persisting in the lung 1 year after cessation of treatment. The clinical and radiographic findings resolve from 3 months to as long as 18 months after cessation of amiodarone [27]. A small percentage of patients with amiodarone lung toxicity have subpleural honeycombing and traction bronchiectasis reflecting usual interstitial pneumonia (UIP) and fibrosis, which is a distinctly different lesion than BOOP [25–27].

Amiodarone BOOP is dose related, and can occur among patients taking 200 mg daily. The duration of therapy prior to symptom onset can be as short as 3 months; however, most cases developed after 2 years and one patient had received 5 years of treatment [28]. Light microscopy shows vacuolization in pneumocyte cytoplasm and electron microscopy shows whorled, lamellar, membranous inclusions in alveolar pneumocytes. Adenopathy may occur in amiodarone-related BOOP [29]. A 67-year-old man had a precardiac transplant evaluation that demonstrated bilateral small parenchymal opacities in the lower lungs and a nodule in the right lower lobe [29]. He developed bilateral ground-glass opacities, and an enlarged precarinal lymph node. Thoracoscopic biopsy showed typical BOOP and abundant foamy macrophages. The amiodarone was discontinued and a chest CT scan 2 months later showed improvement in the lymphadenopathy.

Anti-inflammatory agents that cause BOOP include gold, sulfasalazine, mesalamine, bucillamine and infliximab. Immunosuppressive agents include azathioprine, 6-mercaptopurine, tacrolimus, sirolimus and everolimus [17]. Anticonvulsant agents include carbamazepine and phenytoin. Miscellaneous agents include IFN- $\alpha$ , - $\beta$  and - $\gamma$ , ticlopidine, L-tryptophan, illicit use of cocaine and heroin, fluvastatin, and risidronate [17].

Bronchiolitis obliterans OP can occur in the context of a drug rash with eosinophilia and systemic symptoms, a generalized syndrome that has been associated with anticonvulsant drugs such as carbamazepine and phenytoin [30]. Intravenous heroin can cause BOOP. A 24-year-old woman with 7 years of active intravenous heroin use developed dense bilateral ground glass opacities as confirmed by a chest CT scan and the lung biopsy showed BOOP [31]. After cessation of heroin, respiratory

## Box 2. Bronchiolitis obliterans organizing pneumonia from known causes.

### Post-respiratory infection BOOP

- *Chlamydia*, *Legionella* and *Mycoplasma*
- Adenovirus, cytomegalovirus and influenza virus
- Malaria
- *Pneumocystis*
- *Cryptococcus*
- Hydatid cyst

### Drug-related BOOP

- Antibiotics: minocycline, nitrofurantoin, cephalosporin, amphotericin-B, daptomycin and abacavir
- Cancer chemotherapy drugs: busulfan, methotrexate, bleomycin, doxorubicin, thalidomide, cytosine-arabioside, cytarabine, cyclophosphamide, chlorambucil, rituximab and oxaliplatin
- Cardiovascular drugs: amiodarone and acebutolol
- Anti-inflammatory agents: gold, sulfasalazine, mesalamine or mesalamine, bucillamine and infliximab
- Immunosuppressive agents: azathioprine, 6-mercaptopurine, tacrolimus, sirolimus and everolimus
- Anticonvulsant agents: carbamazepine and phenytoin
- Miscellaneous medications:  $\alpha$ ,  $\beta$  and  $\gamma$  interferons, ticlopidine, L-tryptophan, inhaled cocaine, intravenous heroin, fluvastatin and risidronate

### Radiation therapy BOOP

- Post-breast radiation
- Post-lung cancer and lymphoma radiation

### Organ transplantation BOOP

- Lung, bone marrow, stem cell, renal and liver

### Occupational and environmental BOOP

- Tapestry printing aerosol dye
- House fire smoke
- Food-spice flavoring
- Heated paraffin oil
- Penicillium mold plume
- Goose and duck down pillows and duvets

### Miscellaneous known causes of BOOP

- Aspiration
- Leukemia
- Coronary artery bypass graft surgery
- HIV infection

BOOP: Bronchiolitis obliterans organizing pneumonia.

symptoms subsided without corticosteroid therapy and a follow-up chest CT scan showed marked improvement. Statins may also cause a BOOP reaction as shown by a report of a 66-year-old woman who had 3 weeks of progressive shortness of breath [32]. She had taken fluvastatin for 1 year prior to the onset of dyspnea. She had bilateral crackles and a chest CT scan showing bilateral patchy consolidations. Transbronchial biopsy showed OP and proliferating fibroblasts extending along and branching within alveolar ducts. She had a favorable response with prednisone after cessation of the fluvastatin.

### **Radiation therapy BOOP**

This type usually occurs after breast cancer radiation [17], although it may occur after lung cancer or lymphoma radiation. Symptoms consist of fever and cough [33]; although, there may be no respiratory symptoms and the abnormalities are seen as part of cancer follow-up.

Post-breast radiation BOOP may occur in up to 2.3% of women [34–36]. Majori *et al.* reported spontaneous migration of infiltrates from the irradiated lung to the contralateral non-irradiated lung, and bronchoalveolar lavage showed an increase in lymphocytes, mast cells, CD3 cells, CD8 cells, and a decrease in CD4 cells and the CD4:CD8 ratio [34]. Ogo *et al.* reported a 1.8–2.2% incidence of BOOP among 2056 women receiving radiation therapy for breast carcinoma [35]. Most developed BOOP within 6 months of therapy. Unilateral ground-glass opacities occurred in 70% of patients, and almost always outside the radiation field. In a study of 702 women, 16 (2.3%) of them developed post-radiation BOOP [36]. Risk factors included an age of 50 years or older, and women who had received concurrent endocrine therapy. Tamoxifen was not a risk factor.

### **Organ transplantation BOOP**

This reaction has occurred in association with lung, bone marrow, stem cell, renal and liver transplantation. The fibrotic bronchiolar airway disease constrictive bronchiolitis also occurs in these organ transplant recipients, often more commonly, and is a distinctive lesion not to be confused with BOOP, as the inflammatory BOOP lesion is usually responsive to corticosteroid therapy.

Initially, BOOP in lung transplant recipients was thought to be rare and caused by viral respiratory infections. However, in a study from Denmark of 2697 transbronchial biopsies from 299 lung transplant recipients, BOOP occurred in 28% of lung transplant recipients during the first month and an additional 23% up to 24 months post-lung transplantation [37]. They also demonstrated that BOOP was a risk factor for subsequent pulmonary fibrosis and constrictive bronchiolitis, the concentric, external fibrotic bronchiolar lesion [37,38].

Individuals who have received bone marrow or stem cell transplantation may develop BOOP during the first several months after the procedure [39,40]. Yotsumoto *et al.* found the development of BOOP was between days 22 and 347 with a mean of 114 days [40]. This type may occur from activation of latent and dormant adenovirus or cytomegalovirus, although there may be a genetic basis. Yotsumoto *et al.* found a significantly high frequency ( $p = 0.0069$ ) of HLA B35 among bone marrow transplant recipients who developed BOOP [40].

### **Occupational & environmental BOOP**

The largest report of occupationally-related BOOP involved 22 tapestry air-brush workers in eight textile printing factories in Spain [41,42]. The aerosol dye was implicated in causing the disease, and no new occurrences developed after a change in the spraying process.

There has been a report of a woman who developed BOOP after inhaling smoke during a house fire. BOOP has been reported in a food spice-flavoring process technician [43], in a worker after inhaling metal fumes, and in a worker after inhaling heated paraffin oil.

Exposure to goose or duck feathers used to fill pillows or quilts can cause BOOP [44]. The authors reported 13 individuals who were all women, and symptoms of dyspnea and cough occurred within 3 weeks to 5 years after exposure. Some had previous contact with goose feathers and bird keeping. IgG specific antibodies were detected to goose or duck feathers in all individuals. They had a decreased diffusing capacity, eight with less than 50% predicted. Lavage showed lymphocytosis in all 13 individuals with a mean of 53%. Lung biopsies showed BOOP in two, lymphocytic alveolitis in eight, granulomas in three, and UIP in one patient(s). Inhalation challenge tests were positive in three patients from their own quilts or pillows. A short 4–6-week course of corticosteroid therapy was given with complete recovery observed in seven patients. All individuals improved, some had residual fibrosis [44].

### **Miscellaneous known causes of BOOP**

Aspiration BOOP from gastroesophageal reflux disease has been reported in lung transplant recipients [45]. Particulate matter may also cause aspiration BOOP [46]. Predisposing factors included esophageal or esophageal or gastric causes, drug use and neurological conditions. Foreign material usually included vegetable or food remnants, but also included talc or microcrystalline cellulose, crospovidone and kayexalate [46].

Lymphoma and leukemia BOOP has been reported. Patients with solid organ tumors had nodular or mass-like infiltrates, while the opposite pattern occurred in patients with hematologic malignancies had diffuse infiltrates [47,48]. Coronary artery bypass graft surgery BOOP has been reported. HIV infection BOOP has occurred as a result of the profound effect on the immune system and T-lymphocytes.

### **BOOP associated with systemic disorders**

#### **Rheumatological or connective-tissue BOOP**

Bronchiolitis obliterans OP associated with systemic disorders is listed in Box 3. This type is most commonly found in lupus erythematosus, rheumatoid arthritis and polymyositis/dermatomyositis. It also occurs with scleroderma/progressive systemic sclerosis, ankylosing spondylitis, polymyalgia rheumatica, antisynthetase syndromes, mixed connective tissue disease, Sjögren's syndrome, Sweet's syndrome and Behçet's disease. Chest radiographic findings are similar to the idiopathic type. This type may occur prior to the diagnosis of a connective tissue disorder; therefore, for certain patients, it can be useful to obtain screening blood tests such as the rheumatoid factor, anti-dsDNA antibodies, creatinine phosphokinase, and anticardiolipin antibodies for antiphospholipid syndrome. BOOP has also occurred in juvenile rheumatoid arthritis [49].

Immunological disorders causing BOOP include common variable immunodeficiency syndrome and essential mixed cryoglobulinemia.

**Inflammatory bowel disease BOOP**

This type of BOOP occurs in Crohn's disease and ulcerative colitis. The chest CT scan typically shows patchy infiltrates with air bronchograms [50]. Myelodysplastic syndrome has been a cause of BOOP [51]: BOOP has occurred in Hunner's interstitial cystitis, chronic thyroiditis, alcoholic cirrhosis and primary biliary cirrhosis.

Seasonal BOOP was reported in 12 individuals in the UK [52]. They developed BOOP and liver abnormalities during late February with spontaneous resolution in May, but with recurrence the following year. The cause has not been identified, and may have been due to an inhaled allergen or airborne toxic substance during a specific time of year.

**BOOP associated with underlying lung diseases**

Lung abscess BOOP and lung cancer BOOP have been reported (Box 4).

**BOOP secondary to fibrosing lung disease**

It is necessary to determine if BOOP is part of an underlying lung fibrosing process such as idiopathic pulmonary fibrosis in the form of UIP and nonspecific interstitial pneumonia (NSIP) because the differences in treatment and prognosis are profound [53–55]. The UIP lesion consists of inflammation, fibroblastic foci, traction bronchiectasis and honeycomb lung. The inflammatory component of UIP is usually randomly scattered throughout the lung, but sometimes it has the appearance of organized inflammation in the form of BOOP. In addition, acute exacerbations of UIP may be in the form of BOOP, and these patients have a better response with high-dose corticosteroid therapy than patients with an acute exacerbation showing diffuse alveolar damage [56]. A misdiagnosis of idiopathic BOOP may be made if the tissue from the lung biopsy is too small to show the fibroblastic foci and disruptive lung architecture of UIP. In these situations, BOOP does not progress to a fibrosing process but it is part of the underlying UIP from the beginning. The high-resolution chest CT scan can be used to distinguish the two lesions. For BOOP, there are ground-glass opacities without disruption of the lung architecture, and for UIP, there is traction bronchiectasis and honeycombing.

The BOOP lesion association with NSIP is relatively common and occurs in an individual who has an initial response to corticosteroid therapy but then responds slowly or not at all. It is the same situation as UIP, where the biopsy tissue shows the BOOP lesion, but is too small to show the typical histologic features of NSIP. The high-resolution chest CT scan can be useful to sort out these two disorders owing to the disruption in lung architecture pointing to NSIP.

Distinguishing between these underlying fibrosing lung diseases and BOOP is important to the clinician to be able to predict the clinical course and outcome. Chronic eosinophilic pneumonia and nodular sarcoidosis can have the same radiographic appearance as BOOP, but can be distinguished by histological findings.

**Pathogenesis of BOOP**

The pathogenesis of BOOP is important to understand because it explains why some treatments succeed and others fail. It is an inflammatory lung disease caused by a cascade of cytokine

**Box 3. Bronchiolitis obliterans organizing pneumonia associated with systemic disorders.****Rheumatological or connective-tissue BOOP**

- Rheumatoid arthritis
- Lupus erythematosus
- Polymyositis/dermatomyositis
- Scleroderma/progressive systemic sclerosis
- Ankylosing spondylitis
- Polymyalgia rheumatica
- Antisynthetase syndromes
- Mixed connective tissue disease
- Sjögren's syndrome
- Sweet's syndrome
- Behçet's syndrome

**Immunological disorders**

- Common variable immunodeficiency syndrome
- Essential mixed cryoglobulinemia

**Inflammatory bowel disease**

- Ulcerative colitis
- Crohn's disease

**Myelodysplastic syndrome****Hunner's interstitial cystitis****Chronic thyroiditis****Alcoholic cirrhosis****Primary biliary cirrhosis****Seasonal BOOP with cholestasis**

BOOP: Bronchiolitis obliterans organizing pneumonia.

events and differs from the inflammation occurring in asthma, chronic bronchitis, NSIP and UIP. The pathogenesis is not a fibrotic process as seen in UIP.

Naturally timed apoptosis appears to be a major difference between BOOP and UIP. There is an increased apoptotic activity in BOOP but not UIP [57]. The cytokine profile of BOOP demonstrates an increased degree of macrophage and lymphocyte activation with the T-1 response [58]. In the reovirus model, T-lymphocytic cells have an important role in the pathogenesis, as depletion of CD4<sup>+</sup> or CD8<sup>+</sup> T cells decreases the expression of the proinflammatory cytokines [59].

**Treatment & outcome of the multiple types of BOOP**

Idiopathic BOOP may be monitored if symptoms are mild or radiographic findings and pulmonary function tests do not show severe abnormalities (Box 5). If it worsens, steroid medication can be administered. Most of the time, however, prednisone at 0.5 to 1.0 mg/kg is introduced and is decreased over a 6–12 month period [2]. This usually begins with a 60-mg daily dose until improvement and decreased to 40 mg with decreasing doses pending the clinical course. A 40-mg dose can be administered for less severe disease, and 6 months of treatment may be sufficient for moderate disease [60]. The outcome is good, up to 80% of patients are cured, and a 5% mortality rate continues to be reported. The goal is to administer the least amount of prednisone

**Box 4. Bronchiolitis obliterans organizing pneumonia associated with underlying lung diseases.**

- Lung abscess
- Lung cancer
- Fibrosing lung disease:
  - Idiopathic pulmonary fibrosis/usual interstitial pneumonia
  - Nonspecific interstitial pneumonia

for the shortest possible period of time. Prednisone can be given on an every alternate day dosage schedule, which may decrease its side effects. If the tuberculin test is positive, tuberculosis preventive therapy is needed after ruling out active disease. *Pneumocystis* preventive therapy is needed for prolonged corticosteroid use as well as evaluation for osteoporosis.

One-quarter to one-third of patients may have a relapse requiring an additional course of prednisone therapy. The prednisone can be restarted at 20 mg higher than the dose at relapse. For individuals who relapse at 20 mg or less, the outcome is excellent, while those that relapse at 40 mg or higher have a difficult course. For this latter group, it is helpful to review the high-resolution chest CT scan and biopsy owing to the fact that many of these patients will have NSIP rather than idiopathic BOOP.

For patients who have an initial response to prednisone but later fail to respond, a search must be undertaken for the diagnosis of UIP or NSIP. Other reasons that steroid therapy fails include an atypical type of BOOP or a diagnosis of bronchiolitis interstitial pneumonia [61]. An additional very rare reason for nonresponsive BOOP is dysfunction or loss of the gene responsible for producing the enzyme to metabolize prednisone.

The macrolide antibiotics appear to be helpful in some patients with BOOP [62–65]. In the 1980s, erythromycin at 400 mg daily was found to have a profound influence on the mortality of diffuse panbronchiolitis in Japan reducing the mortality from 90% to less than 15%. In 1993, this form of treatment was found to be effective in six women with BOOP who responded to the treatment

after 3 months of therapy [62]. The anti-inflammatory mechanism includes an increase in the production of  $\beta$ -defensins, a decrease in TNF- $\alpha$  expression and levels, a decrease in IL-8 production and levels, a decrease in release of superoxide and elastase from stimulated neutrophils; impaired phagocytic oxidative neutrophil bursts, decreased neutrophil chemotaxis and survival, and importantly for BOOP, increased apoptosis of lymphocytes as well as increased apoptosis of neutrophils, histiocytes and eosinophils [64,65]. Although, macrolides may be used for patients who cannot be treated with corticosteroid therapy, results may not always be satisfactory. However, for BOOP, azithromycin at 250 mg three-times weekly can be used, and anecdotally may be effective for preventing recurrences. Stover demonstrated that clarithromycin at 250 mg twice daily, can be successful [63].

Immune suppression agents such as cyclophosphamide or azathioprine may be used for patients nonresponsive to corticosteroid therapy. For cyclophosphamide, a 3-month trial at 100–125 mg daily is given. Mycophenolate mofetil (CellCept®), given at 1000-mg doses twice daily, may be helpful in some patients. There have been no large-scale studies demonstrating effectiveness, although these agents may be helpful on a case-by-case basis.

Rapidly progressive BOOP has a poor prognosis and high-dose intravenous corticosteroid therapy is the best available treatment, often in combination with intravenous cyclophosphamide [9]. Focal nodular BOOP may gradually disappear without medications. A brief course of moderate prednisone therapy will result in complete resolution in most individuals. Post-infection BOOP is often responsive to a brief course (weeks) of moderate-to-high dose prednisone therapy. Drug-related BOOP has an excellent outcome. In mild situations, the medication is stopped and BOOP resolves without residual effects. If there are moderate-to-severe symptoms and widespread BOOP, a brief course of a moderate dose of prednisone can be given for complete resolution. Amiodarone BOOP is an exception and may require high-dose prednisone for a longer period of time.

Radiation therapy BOOP has an excellent prognosis that can be monitored for women who have no symptoms or minor symptoms. For women with moderate or severe shortness of breath, a brief course, usually weeks, of a moderate dose of prednisone, usually beginning with 40 mg daily can be administered. Relapses may occur that require additional prednisone. Macrolides have been shown to be helpful in this situation [33].

Occupational and environmental BOOP usually resolves after removal of the causative agent or a brief course of prednisone. Some of the textile workers had residual respiratory dysfunction. Among the 13 individuals with goose or duck down lung disease, a short 4–6-week course of corticosteroid therapy was given with complete recovery in seven patients. All individuals improved, some without BOOP had residual fibrosis [44].

Aspiration BOOP may respond to aggressive treatment of gastroesophageal

**Box 5. Bronchiolitis obliterans organizing pneumonia treatment.**

- Clinical monitoring:
  - No symptoms or mild radiographic findings for certain types of BOOP
- Corticosteroids:
  - Prednisone 40–60 mg daily from 6 to 12 months, and shorter for certain types of BOOP; clinical correlation is recommended
- Macrolides (3-month empiric course for certain types of BOOP):
  - Azithromycin 250 mg three-times weekly
  - Clarithromycin 500 mg twice daily
- Immune suppression agents (3-month empiric course and dosage according to type of BOOP):
  - Cyclophosphamide 100–125 mg daily
  - Azathioprine 100–125 mg daily
  - Mycophenolate mofetil, 1000 mg twice daily

BOOP: Bronchiolitis obliterans organizing pneumonia.

reflux disease. Leukemia- and lymphoma-related BOOP has a good response to prednisone treatment although patients with leukemia may not respond as well as those with solid tumors. AIDS-related BOOP is responsive to prednisone therapy.

Rheumatological or connective-tissue BOOP may respond well to prednisone therapy although the percentage of complete resolution is less than that for the idiopathic form. Inflammatory bowel disease BOOP is usually related to a rapid and sustained clinical improvement with corticosteroid plus prednisone treatment, and some patients can be monitored without treatment. Lung abscess BOOP resolves with antibiotic treatment of the abscess or a small dose of prednisone. Lung cancer BOOP usually responds to the cancer treatment or a brief course of prednisone.

Pulmonary rehabilitation is an important element of managing BOOP as individuals will learn about their disease and learn an exercise program to improve their muscle conditioning, oxygen efficiency and improved sense of control and well being.

In conclusion, there are many types of BOOP and making the distinction among the different types has important clinical application owing to the fact that knowing the different treatments for the multiple types will result in successful management.

### Expert commentary

This section will summarize what I think are some key points for the diagnosis and treatment of the different types of BOOP. For many individuals, BOOP is idiopathic and often presents as a systemic disease with fever and flu-like symptoms. The radiographs may appear more severe than symptoms. The rapidly progressive idiopathic type is severe and associated with high mortality, while the focal nodular type is almost always curable. Most post-respiratory infection BOOP can be treated, but in some situations, it must be recognized early. Amiodarone BOOP continues to be an important drug-related reaction. Post-breast radiation BOOP

occurs in up to 2.3% of women, and can often be treated successfully. The occupational and environmental type continues to be reported sporadically, and duck and goose down usually associated with hypersensitivity pneumonia can cause BOOP. The BOOP lesion associated with UIP and NSIP is an important distinction because this is a secondary lesion and the treatment needs to be directed toward UIP and NSIP. Prednisone continues to be the most optimal treatment for BOOP. The macrolide antibiotics in the form of azithromycin three-times weekly or clarithromycin twice daily may be helpful in some patients. Cyclophosphamide or azathioprine may be used on a case-by-case basis. Mycophenolate mofetil has been used successfully. Pulmonary rehabilitation and an exercise program is a beneficial adjunct for successful treatment.

### Five-year view

Over the next 5 years, I hope to see continued reporting of new and different types of BOOP as this information will be useful to clinicians searching for an answer to the definitive diagnosis. I would also like to see further characterization of BOOP as part of NSIP and UIP, so patients will receive the appropriate diagnosis, therapy, and prognosis. Further delineation of the cascade of cellular events occurring in the pathogenesis will be useful to provide a basis for discovering new treatment. During the next 5 years, I hope to see the optimal setting, dose and duration of macrolide antibiotic treatment for BOOP.

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*The author has no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.*

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### Key issues

- Bronchiolitis obliterans organizing pneumonia (BOOP) is inflammation of the distal bronchioles, respiratory bronchioles, bronchiolar ducts and alveoli.
- Clinical features include cough and shortness of breath and bilateral crackles. The vital capacity is slightly decreased, and the diffusion capacity is moderately to severely decreased.
- The high-resolution chest CT scan shows bilateral ground-glass opacities with air bronchograms, and triangular, pleura-based opacities are almost pathognomonic.
- Idiopathic, amiodarone and post-breast radiation BOOP are important types.
- Corticosteroid therapy is the best treatment option, and the outcome is good, up to 80% of individuals are cured.
- The macrolide antibiotics clarithromycin and azithromycin can be useful in certain situations.
- Immune-suppression agents including cyclophosphamide, azathioprine and mycophenolate mofetil can be useful on a case-by-case basis.

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