CHEST®

Official publication of the American College of Chest Physicians

# Thoracic Manifestations of Inflammatory Bowel Disease*

Hugh Black, Mark Mendoza and Susan Murin

*Chest* 2007;131;524-532
DOI 10.1378/chest.06-1074


ISSN:0012-3692

CHEST

Original Research

INFLAMMATORY BOWEL DISEASE

# Thoracic Manifestations of Inflammatory Bowel Disease*

*Hugh Black, MD; Mark Mendoza, MD; and Susan Murin, MD, MSc, FCCP*

***Background:*** **A growing number of case reports suggest that pulmonary disease occurs in association with inflammatory bowel disease (IBD) more frequently than previously recognized. Screening studies have also identified pulmonary abnormalities in a significant proportion of IBD patients.**

***Methods:*** **A focused literature review of respiratory abnormalities in IBD patients and 55 English-language case series documenting 171 instances of respiratory pathology in 155 patients with known IBD.**

***Results:*** **Screening studies using respiratory symptoms, high-resolution CT, and pulmonary function testing support a high prevalence of respiratory abnormalities among patients with IBD. Case reports and series document a spectrum of respiratory system involvement that spans from larynx to pleura, with bronchiectasis as the single most common disorder. IBD patients have a threefold risk of venous thromboembolism, and recent investigations have also revealed possible ties between IBD and other diseases involving the respiratory system, including sarcoidosis, asthma, and $\alpha_1$-antitrypsin deficiency.**

***Conclusion:*** **Respiratory symptoms and diagnosed respiratory system disorders are more common among patients with IBD than generally appreciated. The spectrum of respiratory disorders occurring among patients with IBD is very broad. Diseases of the large airways are the most common form of involvement, with bronchiectasis being the most frequently reported form of IBD-associated lung disease.** ***(CHEST 2007; 131:524–532)***

**Key words:** bronchiectasis; bronchiolitis obliterans; bronchiolitis obliterans organizing pneumonia; Crohn disease; inflammatory bowel disease; sarcoidosis; tracheitis; ulcerative colitis

**Abbreviations:** BOOP = bronchiolitis obliterans organizing pneumonia; CD = Crohn disease; DLCO = diffusing capacity of the lung for carbon monoxide; HLA = human leukocyte antigen; HRCT = high-resolution CT; IBD = inflammatory bowel disease; PFT = pulmonary function testing; UC = ulcerative colitis; VTE = venous thromboembolism

The inflammatory bowel diseases (IBDs), Crohn disease (CD) and ulcerative colitis (UC), are widely recognized disorders of the GI tract that may have a variety of extraintestinal manifestations. These include pyoderma gangrenosum, erythema nodosum, uveitis, episcleritis, cholestatic liver disease, hemolytic anemia, arthritis, and pulmonary disease of various types.[1] A link between pulmonary disease and IBD was suggested nearly 40 years ago.[2] Both screening studies and the cumulative volume of case reports suggest that the respiratory system may be involved in IBD more frequently than is generally appreciated. Thoracic pathology in this population is extremely varied, and individual patients may manifest pulmonary abnormalities at multiple sites.

Commonality between the GI and respiratory systems provides some pathophysiologic basis for respiratory involvement in IBD. Both the colonic and respiratory epithelia share embryonic origin from the primitive foregut. Both possess goblet cells

*From the Division of Pulmonary and Critical Care Medicine, University of California at Davis School of Medicine, Davis, CA.
None of the authors of this article have any conflicts of interest to disclose.
Manuscript received April 21, 2006; revision accepted August 8, 2006.

*Correspondence to: Susan Murin, MD, MSc, Department of Internal Medicine, Division of Pulmonary and Critical Care Medicine, University of California at Davis School of Medicine, 4150 V St, Suite 3400, Sacramento, CA 95817; e-mail: sxmurin@ucdavis.edu*
**DOI: 10.1378/chest.06-1074**

and submucosal glands as part of their lumenal structure. In addition, both lung and GI tract contain submucosal lymphoid tissue and play crucial roles in host mucosal defense. The aberrations in both innate and acquired immunity that are involved in the pathogenesis of IBD are complex and still incompletely understood.[3] In addition, many of the reported pulmonary diseases associated with IBD have cryptic etiologies. Thus, at this time the causes or mechanisms of various forms of respiratory tract involvement in IBD remain poorly understood.

In this article, we review the thoracic manifestations of IBD. First, various approaches to the identification of pulmonary disease in IBD patients are discussed. Next, thoracic findings culled from > 50 case series identified via a focused literature review are summarized and organized according to the anatomic location of respiratory involvement. The relationships between IBD and sarcoidosis, $\alpha_1$-antitrypsin deficiency, and venous thromboembolism (VTE) are discussed. Pulmonary effects of pharmacologic therapies for IBD have been examined elsewhere[4] and are beyond the scope of this review.

## Materials and Methods

Medline searches using the terms "inflammatory bowel disease," "ulcerative colitis," and "Crohn's disease," in conjunction with the terms "lung," "pulmonary," "bronchiectasis," "bronchitis," "sarcoidosis," "bronchiolitis obliterans organizing pneumonia," "venous thromboembolism," "pulmonary embolism," "pericarditis," "interstitial lung disease," "alpha-1 anti-trypsin deficiency," and "asthma" were performed. Articles focused on infections, pathologies attributable to coexistent disease, and complications of therapy were excluded, as were those that were not in English. All applicable, retrievable manuscripts were reviewed by the authors, and data were abstracted. Articles not available in the University of California, Davis Library or UC Digital Library were requested through interlibrary loan services; > 95% of all citations were retrievable. The references of the various articles retrieved from the above process were themselves reviewed for additional citations. Relevant data were abstracted and entered into an Excel file (Microsoft; Redmond, WA) for summary and analysis. References for case reports not included have been placed in the Appendix at the end of this article.

## Pulmonary Disease in IBD Patients

### *Respiratory Symptoms*

The prevalence of respiratory symptoms in IBD patients without pulmonary pathology has been examined in a number of small studies. Among 44 randomly selected IBD patients, Douglas et al[5] found that 48% had unspecified respiratory symptoms. Songur et al[6] found that 16 of 36 IBD patients (44%) in a gastroenterology clinic had symptoms of wheeze, cough, sputum production, or breathlessness. Finally, Ceyhan and others[7] found 15 of 30 consecutively surveyed IBD patients had symptoms of dyspnea, cough, sputum, or wheeze for > 1 month. These investigations, while limited in scope, suggest that patients with IBD have pulmonary symptoms with greater frequency than the general population (Table 1).[5–25]

### *High-Resolution CT Findings*

High-resolution CT (HRCT) scanning has been used to screen for latent pulmonary disease in IBD patients. A single-center study[8] of 15 asymptomatic patients with UC identified subtle HRCT abnormalities in 25% of patients. A subsequent case control study[6] found subtle HRCT abnormalities in a majority of screened IBD patients but none among control subjects (n = 14; 53% vs 0%, respectively). The spectrum of reported HRCT abnormalities in these patients includes air-trapping, ground-glass opacification, peripheral reticular opacities, and cysts.

### *Pulmonary Function*

A number of investigations have focused on results of pulmonary function testing (PFT) among patients with IBD. Case-control studies designed to investigate the hypothesis that IBD is associated with abnormal pulmonary function have been limited by low numbers of patients and poor choice of control subjects. An early investigation[26] found no difference in pulmonary function between IBD patients and control subjects, but it may have lacked adequate statistical power. Subsequent studies have consistently found subtle abnormalities in pulmonary function in IBD patients.

A number of reports[6,9–13] have demonstrated a decrease in diffusion capacity of the lung for carbon monoxide (Dlco) between asymptomatic IBD patients and control subjects. The first large study to

**Table 1—*Evidence of Pulmonary Involvement in IBD Patients***

| |
|---|
| Increased respiratory symptoms[5–7] |
| Wheeze, cough, sputum production, breathlessness |
| Abnormal HRCT findings[6,8] |
| Air-trapping, ground-glass opacification, peripheral reticular opacities, cysts |
| Abnormal PFT results |
| Decreased Dlco[6,9–13,25] |
| Hyperinflation[5,6,14] |
| Increased response to methacholine[15–17] |
| BAL lymphocytosis[18–21] |
| Epidemiologic data |
| Increased prevalence of asthma[22] |
| Increased prevalence of VTE[23,24] |

illustrate this was that of Heatley and colleagues,[25] and those findings have since been corroborated.[6,9–13] Interestingly, two studies by Tzanakis et al[11,27] have shown that DLCO is significantly lower among IBD patients with active GI disease than those in remission. Marvisi et al[12] reported a similar finding in a smaller cohort with UC. This suggests that degree of GI inflammation may correlate with the severity of lung disease in these patients, but this hypothesis has yet to be confirmed in a longitudinal cohort study.

A number of studies have been performed to assess airflow obstruction in patients with IBD, with conflicting results. Herrlinger and colleagues[13] found decrements in $FEV_1$ in IBD patients compared to control subjects, but the magnitude of difference was small and the absolute value of $FEV_1$ in both groups was normal. More UC patients than control subjects were found to have obstruction during PFT in a series of 100 subjects,[28] but cases and control subjects were not matched for age or smoking status. Most studies have not found evidence of obstruction using conventional spirometric parameters.

Other reports have employed less conventional measures of airflow obstruction to identify subclinical pulmonary disease. Utilizing a measurement of the volume at which flow of oxygen and helium became equal as a indication of small airways function, Tzanakis et al[27] have shown an increased prevalence of small airway dysfunction among IBD patients. In addition, patients with active UC had increased airway obstruction compared with patients with inactive UC. Pasquis et al[14] found an increase in functional residual capacity among a small number of patients with CD. Two other investigations[5,6] have also found evidence of hyperinflation, as assessed by functional residual capacity and residual volume, among patients with IBD. Furthermore, there was an association between hyperinflation and active IBD in this cohort. Muscle weakness and steroid myopathy may be confounders of this variable, given the frequent use of steroid treatment for IBD. Two groups, Mansi and colleagues[17] and Louis et al[15,16] have documented increased bronchial response to methacholine, a measure of airway hyperactivity, among patients with both CD and UC[15] and CD,[16,17] but this was not confirmed in another study[7] of similar design.

### *Bronchoscopy*

The presence of chronic inflammation in the lungs of IBD patients has also been documented by cellular analysis of BAL fluid from IBD patients. Investigators at the University of Lille found increased alveolar lymphocytosis on BAL in a cohort of 18 asymptomatic subjects with CD compared to 25 control subjects,[18] and in another case-control study[19] with 22 asymptomatic subjects with CD and 25 control subjects.

## Survey of Case Report Literature

A search using the PubMed database identified 55 English-language articles documenting thoracic findings in 155 patients with known IBD. These are organized according to site of involvement within the respiratory system and are presented in Table 2.

### *Airway Disease*

The large airways are the most common location of IBD involvement, accounting for 39% of all cases reviewed.[29–31,40–53] Respiratory disease tends to occur in the fifth decade of life, although a there is a wide range of ages of onset. Most patients are female, and nearly all patients have UC. In only four cases has large airway disease been reported to predate GI disease, and the age of disease onset in these patients is notably younger ($13 \pm 7.5$ years [$\pm$ SD]). Patients with large airways disease may also have coincident nonthoracic extraintestinal manifestations, including microangiopathic hemolytic anemia, pyoderma gangrenosum, primary sclerosing cholangitis, episcleritis, and peripheral and axial arthritis.

Bronchiectasis is the classic pulmonary manifestation of IBD, noted in 66% of instances of IBD involving the large airways (Fig 1). Other abnormalities of the large airways include chronic bronchitis, suppurative large airway disease without airway dilation, and acute bronchitis. A surprisingly high proportion of these patients are nonsmokers (81%).

Interestingly, nine patients, mostly with UC, presented with or had a recrudescence of bronchiectasis within 1 year of colectomy. In one case, bronchiectasis presented within weeks of colectomy. This temporal link between colonic resection and onset or worsening of pulmonary disease has fueled speculation that colectomy may actually induce pulmonary disease in these patients.[88] Alternatively, this phenomenon may be related to the discontinuation of immunosuppressive therapies after presumed surgical cure of the disease.

Clinically, small airways are rarely affected in IBD. However, the recent advent of HRCT has increased the detection small airway involvement in these patients. HRCT abnormalities consistent with small airways abnormalities have been described in symptomatic IBD patients, some with normal PFT findings.[52]

**Table 2—*Summary of Reported Cases of Thoracic Involvement in IBD**

| Site of Involvement | Cases, No. | Mean Age ± SD, yr | Female Gender, % | UC, % | Extraintestinal Manifestations, % |
|---|---|---|---|---|---|
| Upper airway[29–39] | 15 | 40.5 ± 14.8 | 40 | 73.3 | 33.3 |
| Trachea | 15 | | | | |
| Larynx/glottis | 2 | | | | |
| Large airways[29–31,40–53] | 67 | 42.6 ± 7.4 | 64.2 | 89 | 52 |
| Bronchiectasis | 44 | | | | |
| Chronic bronchitis | 13 | | | | |
| Suppurative airway disease | 5 | | | | |
| Acute bronchitis | 2 | | | | |
| Small airways[32,46,50,54–61] | 17 | 28.9 ± 14.4 | 47 | 53 | 18.1 |
| Bronchiolitis | 10 | | | | |
| Bronchiolitis obliterans | 6 | | | | |
| Diffuse panbronchiolitis | 1 | | | | |
| Parenchyma[30,45,46,53,56,61–76] | 40 | 38.8 ± 21.2 | 57.5 | 64.9 | 32.5 |
| BOOP | 21 | | | | |
| Nodules | 6 | | | | |
| Interstitial lung disease not otherwise specified | 6 | | | | |
| Pulmonary interstitial emphysema | 3 | | | | |
| Desquamative interstitial pneumonia | 1 | | | | |
| Nonspecific interstitial pneumonia | 1 | | | | |
| Fibrosing alveolitis | 1 | | | | |
| Eosinophilic pneumonitis | 1 | | | | |
| Sarcoidosis | NS | | | | |
| α1-Antitrypsen deficiency | NS | | | | |
| Pulmonary vasculature[30,60,73–75,77–81] | 10 | 29.3 ± 13.9 | 50 | 90 | 30 |
| Wegener granulomatosis | 3 | | | | |
| Churg-Strauss syndrome | 1 | | | | |
| Microscopic polyangiitis | 2 | | | | |
| Pulmonary vasculitis not otherwise specified | 4 | | | | |
| Serosa[30,59,65–67,73–75,82–87] | 22 | 29 ± 14 | 37 | 73 | 31.8 |
| Pleural disease | 12 | | | | |
| Pericardial disease | 15 | | | | |

*NS = not significant.

Small airway involvement in IBD tends to present at a younger age and at an earlier point in the disease course than abnormalities of the large airways.[32,46,50,54–61] In contrast to other airway manifestations, diseases of the small airways more commonly occur before symptomatic GI disease (29% of surveyed cases). Pathologically, bronchiolitis is the most commonly reported disease involving the small airways in patients with IBD. Pathology frequently shows peribronchiolar granuloma formation (58.8%). Less frequent findings include peribronchiolar inflammation with either neutrophils or lymphocytes and plasma cells, concentric small airway fibrosis, and diffuse panbronchiolitis.

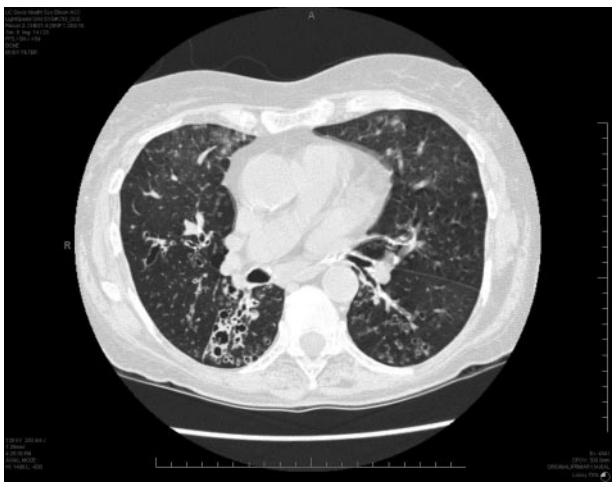

FIGURE 1. CT showing bronchiectasis and inflammatory nodules in a 72-year-old woman with UC.

Upper airway involvement comprises the remainder of IBD-related airways disease. We review 15 cases of this rare entity.[29–39] All cases of upper airway involvement involve the trachea, although two cases of laryngeal and glottic disease occurring concomitantly with tracheal lesions have been reported. One patient required tracheal dilation but eventually succumbed to barotrauma after repeated dilations.[32]

Steroids are the major therapy involved in the treatment of airways disease in patients with IBD (65%), although some of these patients do not require systemic therapy. Clinical improvement with inhaled steroids alone or in combination with sys-

temic steroids has been reported. Rarely, other forms of immune modulation have been used to treat IBD-related airway disease.[50,53]

*Asthma:* Recent data suggest that IBD may be associated with asthma to a far greater extent than had previously been considered. A population-based cohort study[22] at the University of Manitoba documented an increased prevalence of asthma among 8,072 UC patients compared with 41,815 control subjects matched for age, sex, and postal location. Furthermore, a number of studies document an association between IBD and various allergic diseases. D'Arienzo and colleagues[89] showed an increased propensity for allergic disease identified by family history, skin-prick testing, and prior diagnosis of allergic disease among 45 patients with UC compared to 37 control subjects. Increased levels of tumor necrosis factor-α and increased mast cell activity are common to both atopy and IBD, and have been suggested as the link between them.[90]

Other investigations have focused on the intersection between allergic and airway disease in IBD patients. Ceyhan and colleagues[7] found increased allergic symptoms, increased prevalence of positive skin-prick test results, higher IgE levels, and more abnormal pulmonary function among 30 IBD patients compared with control subjects. Louis and colleagues[16] also documented increased response to methacholine and sputum eosinophils among CD patients. Increased bronchial hyperresponsiveness on methacholine challenge was also documented in 14 children with CD compared to control subjects, although the provocative dose causing a 20% fall in $FEV_1$ in CD patients was greater than in the 10 asthmatics also tested in the study.[17]

There is evidence that asthma has a more severe course in IBD patients. A population-based cohort study in Stockholm found a sixfold increase in the number of deaths caused by asthma among 1,547 patients with UC compared with sex-specific death rates from the National Cause-of-Death Register.[91] Finally, patients with UC and asthma have increased airway obstruction and a lower provocative concentration causing a 20% fall in $FEV_1$ on methacholine challenge compared to asthmatics without UC.[92] This same cohort of patients also demonstrated increased sputum concentration of vascular endothelial growth factor, leading the authors to propose a more pronounced inflammatory cascade, increased vascular endothelial growth factor activity, and vascular permeability in UC patients with asthma. Further investigation is needed to better elucidate this connection.

*Parenchymal Disease*

Lung disease involving the pulmonary parenchyma is relatively uncommon among IBD patients. Those cases that have been reported reveal a wide range of pathologies. Analysis of diffuse lung disease in IBD patients is further confounded by documented pulmonary sequelae to various medical therapies used to treat IBD. Findings discussed below were attributed by their authors to IBD and not to medications used in its treatment.[30,45,46,53,56,61,62–76]

UC is the underlying form of IBD in the majority of reported cases of IBD-associated parenchymal lung disease. Age of onset varies, and there is a slight female predominance. Bronchiolitis obliterans organizing pneumonia (BOOP) is the most commonly reported parenchymal manifestation of IBD. As with non–IBD-related BOOP, resolution with systemic steroids is the norm, although disease may remit without treatment in a minority of cases (21%). A single report[76] documented resolution of BOOP with infliximab after a failure of steroid therapy. Other forms of diffuse lung disease reported among patients with IBD include pulmonary interstitial emphysema syndrome, desquamative interstitial pneumonia, nonspecific interstitial pneumonia, fibrosing alveolitis, and eosinophilic pneumonitis. Pulmonary nodules have been infrequently reported in patients with IBD. Histologically, these lesions have been reported to be necrobiotic (25%), granulomatous (12.5%), or otherwise.

*Sarcoidosis:* IBD and sarcoidosis are usually considered to be distinct entities. However, the cumulative volume of case reports documenting coexistence of these two entities suggests a link between them. Storch et al[93] documented 46 cases of IBD and concomitant sarcoidosis in a review of the literature in 2003. We have identified seven more reports[76,94–98] of this association, bringing the total reported cases of coexisting disease to 53.

The pathophysiologic basis of a relationship between IBD and sarcoidosis is unclear. Genetic susceptibility and derangements of cellular immunity play important roles in the development of both. Barr et al[99] reported that human leukocyte antigen (HLA)-B8 and HLA-DR3 haplotypes were present in three of eight patients with UC and sarcoidosis, a higher proportion than expected. Papadopoulos et al[100] reported a greater incidence of a variety of autoimmune diseases in patients with sarcoidosis, and suggested that HLA-linked genetic susceptibility (HLA-B8/DR3) predisposes sarcoidosis patients to a variety of autoimmune diseases. Finally, IBD and

sarcoidosis share comparable dermatologic, ocular, and joint manifestations, further suggesting a pathogenic link.

Nontuberculous Mycobacterium species have been postulated as an infectious cause of, and have been detected in tissues from patients with, both IBD and sarcoid.[101] Elevated CD4:CD8 ratios on BAL, a characteristic but not diagnostic finding in sarcoidosis, have also been documented in patients with CD.[20,21] Serum angiotensin-converting enzyme levels, while often increased in several granulomatous diseases such as sarcoidosis, leprosy, Gaucher disease, histoplasmosis, and extrinsic allergic alveolitis, remain low in CD.[102]

*$\alpha_1$-Antitrypsin Deficiency:* A single case report[103] of colitis and coincident emphysema noted in the 1980s has led to the recent hypothesis that, like emphysema, disregulation of protease activity may be involved in the pathogenesis of IBD. Fecal clearance of $\alpha_1$-antitrypsin has been used as an indicator of severity of disease in IBD. A number of studies[104–106] have investigated the prevalence of abnormal $\alpha_1$-antitrypsin alleles in patients with IBD, with mixed results. In the only study with positive results of its kind, Elzouki and colleagues[105] documented a greater prevalence of PiZ carriers among patients with IBD vs that expected in the general population (8.5% vs 4.7%), and an increased extent and severity of colitis in association with PiZ carrier status. Subsequently, a group at the Mayo Clinic have identified an additional 10 patients, 7 with emphysema, who had concomitant $\alpha_1$-antitrypsen deficiency and IBD.[107] Combined with the complex effects of smoking on the prevalence and course of UC and CD, this observation has lead the authors to propose that, as in the lung, imbalances in neutrophil elastase regulation exhibited in $\alpha_1$-antitrypsin deficiency may enhance potential local tissue damage in the gastroenterological tract from smoking. Further investigation is needed to better elucidate this connection.

### *Pulmonary Vascular Disease*

Vascular disease rarely occurs with IBD.[30,60,73–75,77–81] Wegener granulomatosis, Churg-Strauss syndrome, microscopic polyangiitis, and pulmonary vasculitis have been reported. Nearly all cases have coexisting cholangitis or arthritis. Systemic steroids are the mainstay of therapy, although a patient with Churg-Strauss syndrome also received cytoxan.[81]

*VTE:* Patients with inflammatory bowel disease are at increased risk of thromboembolic disease. The incidence of thromboembolic events appears to be three to four times higher for patients with IBD compared with age-matched control subjects.[23,24] The majority of thromboembolic events among IBD patients are VTE, manifested as either deep venous thrombosis or pulmonary embolism, but arterial thromboembolism and venous thrombosis at unusual sites have also been reported.[108]

The pathogenesis of increased thrombotic risk among patients with IBD is unclear. The prevalence of inherited prothrombotic disorders is no higher among patients with IBD than in the general population. While laboratory markers of activation of the coagulation system have been found in some patients with IBD,[109–113] the significance of this finding is unclear. IBD patients often have acquired thrombosis risk factors in conjunction with their disease or its treatment, including immobility, surgery, and central venous catheters. However, up to one third of thrombotic events among IBD patients occur while their disease is quiescent, suggesting ongoing thrombotic risk unrelated to disease activity or therapy.[110]

### *Serositis*

Pleural and pericardial manifestations of IBD are uncommon.[30,59,65–67,73–75,82–87] Most patients are young, male, and have UC. Pleural involvement is nearly always unilateral; when examined, pleural fluid tends to be exudative in nature.[29] Direct inspection of pleural surfaces reveals thickening and inflammation.[59,75] In a single case in which pleural biopsy was reported, nonspecific inflammation without granulomas was found.[65] The pericardium is uniquely involved in 45% of cases, and many of these patients also received systemic steroids, although two patients were treated with nonsteroidal antiinflammatory drugs (aspirin or indocin). A single case of cardiac tamponade requiring pericardial drainage has been reported. Coincident pleural and pericardial involvement has been documented in a minority of cases.

## Conclusion

Screening studies using respiratory symptoms, HRCT, and PFT support a high prevalence of respiratory abnormalities among patients with IBD. The cumulative volume of published case reports suggests that respiratory manifestations of IBD are more common than generally appreciated and are quite varied. Bronchiectasis is the most common form of respiratory tract abnormality seen among patients with IBD, but the spectrum of involvement spans the entire respiratory system, from larynx to pleura. Most cases of respiratory tract disease occur

years after the diagnosis of IBD, but occasionally the respiratory tract disease precedes the diagnosis. IBD patients have an increased risk for VTE. In addition, there may also be links between IBD and sarcoidosis, asthma, and $\alpha_1$-antitrypsin deficiency. Steroids are the most frequently reported treatment used for pulmonary disease associated with IBD, but controlled trials confirming their efficacy are lacking.

## Appendix


Bar-Dayan Y, Ben-Zikrie S, Fraser G, et al. Pulmonary alveolar hemorrhage in a patient with ulcerative colitis and primary sclerosing cholangitis. Isr Med Assoc J 2002; 4:464–465

Baron FA, Hermanne JP, Dowlati A, et al. Bronchiolitis obliterans organizing pneumonia and ulcerative colitis after allogeneic bone marrow transplantation. Bone Marrow Transplant 1998; 21:951–954

Chikano S, Sawada K, Ohnishi K, et al. Interstitial pneumonia accompanying ulcerative colitis. Intern Med 2001; 40:883–886

Codish S, Abu-Shakra M, Depsames R, et al. Wegener's granulomatosis in a patient with Crohn's disease. Isr Med Assoc J 2000; 2:630–631

Dawson A, Gibbs AR, Anderson G. An unusual perilobular pattern of pulmonary interstitial fibrosis associated with Crohn's disease. Histopathology 1993; 23:553–556

Kar PM, Aronoff G, Schuette P. Bronchopulmonary disease: an association with ulcerative colitis and pyoderma gangrenosum. J Kedziora JA, Wolff M, Chang J. Limited form of Wegener's granulomatosis in ulcerative colitis. Am J Roentgenol Radium Ther Nucl Med 1975; 125:127–133 Ky Med Assoc 1993; 91:320–323

Kuzela L, Vavrecka A, Prikazska M, et al. Pulmonary complications in patients with inflammatory bowel disease. Hepatogastroenterology 1999; 46:1714–1719


## References


1 Levine JB, Lukawski-Trubish D. Extraintestinal considerations in inflammatory bowel disease. Gastroenterol Clin North Am 1995; 24:633–646

2 Turner-Warwick M. Fibrosing alveolitis and chronic liver disease. Q J Med 1968; 37:133–149

3 Bamias G, Nyce MR, De La Rue SA, et al. New concepts in the pathophysiology of inflammatory bowel disease. Ann Intern Med 2005; 143:895–904

4 Parry SD, Barbatzas C, Peel ET, et al. Sulphasalazine and lung toxicity. Eur Respir J 2002; 19:756–764

5 Douglas JG, McDonald CF, Leslie MJ, et al. Respiratory impairment in inflammatory bowel disease: does it vary with disease activity? Respir Med 1989; 83:389–394

6 Songur N, Songur Y, Tuzun M, et al. Pulmonary function tests and high-resolution CT in the detection of pulmonary involvement in inflammatory bowel disease. J Clin Gastroenterol 2003; 37:292–298

7 Ceyhan BB, Karakurt S, Cevik H, et al. Bronchial hyperreactivity and allergic status in inflammatory bowel disease. Respiration 2003; 70:60–66

8 Karadag F, Ozhan MH, Akcicek E, et al. Is it possible to detect ulcerative colitis-related respiratory syndrome early? Respirology 2001; 6:341–346

9 Eade OE, Smith CL, Alexander JR, et al. Pulmonary function in patients with inflammatory bowel disease. Am J Gastroenterol 1980; 73:154–156

10 Neilly JB, Main AN, McSharry C, et al. Pulmonary abnormalities in Crohn's disease. Respir Med 1989; 83:487–491

11 Tzanakis N, Bouros D, Samiou M, et al. Lung function in patients with inflammatory bowel disease. Respir Med 1998; 92:516–522

12 Marvisi M, Borrello PD, Brianti M, et al. Changes in the carbon monoxide diffusing capacity of the lung in ulcerative colitis. Eur Respir J 2000; 16:965–968

13 Herrlinger KR, Noftz MK, Dalhoff K, et al. Alterations in pulmonary function in inflammatory bowel disease are frequent and persist during remission. Am J Gastroenterol 2002; 97:377–381

14 Pasquis P, Colin R, Denis P, et al. Transient pulmonary impairment during attacks of Crohn's disease. Respiration 1981; 41:56–59

15 Louis E, Louis R, Drion V, et al. Increased frequency of bronchial hyperresponsiveness in patients with inflammatory bowel disease. Allergy 1995; 50:729–733

16 Louis E, Louis R, Shute J, et al. Bronchial eosinophilic infiltration in Crohn's disease in the absence of pulmonary disease. Clin Exp Allergy 1999; 29:660–666

17 Mansi A, Cucchiara S, Greco L, et al. Bronchial hyperresponsiveness in children and adolescents with Crohn's disease. Am J Respir Crit Care Med 2000; 161:1051–1054

18 Wallaert B, Colombel JF, Tonnel AB, et al. Evidence of lymphocyte alveolitis in Crohn's disease. Chest 1985; 87: 363–367

19 Bonniere P, Wallaert B, Cortot A, et al. Latent pulmonary involvement in Crohn's disease: biological, functional, bronchoalveolar lavage and scintigraphic studies. Gut 1986; 27:919–925

20 Bewig B, Manske I, Bottcher H, et al. Crohn's disease mimicking sarcoidosis in bronchoalveolar lavage. Respiration 1999; 66:467–469

21 Smiejan JM, Cosnes J, Chollet-Martin S, et al. Sarcoid-like lymphocytosis of the lower respiratory tract in patients with active Crohn's disease. Ann Intern Med 1986; 104:17–21

22 Bernstein CN, Wajda A, Blanchard JF. The clustering of other chronic inflammatory diseases in inflammatory bowel disease: a population-based study. Gastroenterology 2005; 129:827–836

23 Miehsler W, Reinisch W, Valic E, et al. Is inflammatory bowel disease an independent and disease specific risk factor for thromboembolism? Gut 2004; 53:542–548

24 Bernstein CN, Blanchard JF, Houston DS, et al. The incidence of deep venous thrombosis and pulmonary embolism among patients with inflammatory bowel disease: a population-based cohort study. Thromb Haemost 2001; 85:430–434

25 Heatley RV, Thomas P, Prokipchuk EJ, et al. Pulmonary function abnormalities in patients with inflammatory bowel disease. Q J Med 1982; 51:241–250

26 Johnson NM, Mee AS, Jewell DP, et al. Pulmonary function in inflammatory bowel disease. Digestion 1978; 18:416–418

27 Tzanakis N, Samiou M, Bouros D, et al. Small airways function in patients with inflammatory bowel disease. Am J Respir Crit Care Med 1998; 157:382–386

28 Godet PG, Cowie R, Woodman RC, et al. Pulmonary function abnormalities in patients with ulcerative colitis. Am J Gastroenterol 1997; 92:1154–1156

29 Lemann M, Messing B, D'Agay F, et al. Crohn's disease with respiratory tract involvement. Gut 1987; 28:1669–1672

30 Camus P, Piard F, Ashcroft T, et al. The lung in inflammatory bowel disease. Medicine (Baltimore) 1993; 72:151–183

31 Garg K, Lynch DA, Newell JD. Inflammatory airways disease in ulcerative colitis: CT and high-resolution CT features. J Thorac Imaging 1993; 8:159–163

32 Wilcox P, Miller R, Miller G, et al. Airway involvement in ulcerative colitis. Chest 1987; 92:18–22
33 Iwama T, Higuchi T, Imajo M, et al. Tracheo-bronchitis as a complication of Crohn's disease: a case report. Jpn J Surg 1991; 21:454–457
34 Vasishta S, Wood JB, McGinty F. Ulcerative tracheobronchitis years after colectomy for ulcerative colitis. Chest 1994; 106:1279–1281
35 Lamblin C, Copin MC, Billaut C, et al. Acute respiratory failure due to tracheobronchial involvement in Crohn's disease. Eur Respir J 1996; 9:2176–2178
36 Kuzniar T, Sleiman C, Brugiere O, et al. Severe tracheobronchial stenosis in a patient with Crohn's disease. Eur Respir J 2000; 15:209–212
37 Shad JA, Sharieff GQ. Tracheobronchitis as an initial presentation of ulcerative colitis. J Clin Gastroenterol 2001; 33:161–163
38 Rickli H, Fretz C, Hoffman M, et al. Severe inflammatory upper airway stenosis in ulcerative colitis. Eur Respir J 1994; 7:1899–1902
39 Janssen WJ, Bierig LN, Beuther DA, et al. Stridor in a 47-year-old man with inflammatory bowel disease. Chest 2006; 129:1100–1106
40 Kraft SC, Earle RH, Roesler M, et al. Unexplained bronchopulmonary disease with inflammatory bowel disease. Arch Intern Med 1976; 136:454–459
41 Butland RJ, Cole P, Citron KM, et al. Chronic bronchial suppuration and inflammatory bowel disease. Q J Med 1981; 50:63–75
42 Shneerson JM. Lung bullae, bronchiectasis, and Hashimoto's disease associated with ulcerative colitis treated by colectomy. Thorax 1981; 36:313–314
43 Gibb WR, Dhillon DP, Zilkha KJ, et al. Bronchiectasis with ulcerative colitis and myelopathy. Thorax 1987; 42:155–156
44 Moles KW, Varghese G, Hayes JR. Pulmonary involvement in ulcerative colitis. Br J Dis Chest 1988; 82:79–83
45 Gabazza EC, Taguchi O, Yamakami T, et al. Bronchopulmonary disease in ulcerative colitis. Intern Med 1992; 31:1155–1159
46 Mazer BD, Eigen H, Gelfand EW, et al. Remission of interstitial lung disease following therapy of associated ulcerative colitis. Pediatr Pulmonol 1993; 15:55–59
47 Eaton TE, Lambie N, Wells AU. Bronchiectasis following colectomy for Crohn's disease. Thorax 1998; 53:529–531
48 Spira A, Grossman R, Balter M. Large airway disease associated with inflammatory bowel disease. Chest 1998; 113:1723–1726
49 Leon EE, Clark T, Craig TJ. Bronchiectasis in a 33-year-old male with ulcerative colitis. Ann Allergy Asthma Immunol 1999; 83:505–509
50 Ward H, Fisher KL, Waghray R, et al. Constrictive bronchiolitis and ulcerative colitis. Can Respir J 1999; 6:197–200
51 Akobeng AK, Miller V, Thomas AG. Unexplained chronic bronchial suppuration and inflammatory bowel disease. J Pediatr Gastroenterol Nutr 1999; 28:324–326
52 Mahadeva R, Walsh G, Flower CD, et al. Clinical and radiological characteristics of lung disease in inflammatory bowel disease. Eur Respir J 2000; 15:41–48
53 Alrashid AI, Brown RD, Mihalov ML, et al. Crohn's disease involving the lung: resolution with infliximab. Dig Dis Sci 2001; 46:1736–1739
54 Desai SJ, Gephardt GN, Stoller JK. Diffuse panbronchiolitis preceding ulcerative colitis. Chest 1989; 95:1342–1344
55 Hilling GA, Robertson DA, Chalmers AH, et al. Unusual pulmonary complication of ulcerative colitis with a rapid response to corticosteroids: case report. Gut 1994; 35:847–848
56 Veloso FT, Rodrigues H, Aguiar MM. Bronchiolitis obliterans in ulcerative colitis. J Clin Gastroenterol 1994; 19:339–341
57 Vandenplas O, Casel S, Delos M, et al. Granulomatous bronchiolitis associated with Crohn's disease. Am J Respir Crit Care Med 1998; 158:1676–1679
58 Bentur L, Lachter J, Koren I, et al. Severe pulmonary disease in association with Crohn's disease in a 13-year-old girl. Pediatr Pulmonol 2000; 29:151–154
59 Haralambou G, Teirstein AS, Gil J, et al. Bronchiolitis obliterans in a patient with ulcerative colitis receiving mesalamine. Mt Sinai J Med 2001; 68:384–388
60 Yano S, Kobayashi K, Kato K, et al. A limited form of Wegener's granulomatosis with bronchiolitis obliterans organizing pneumonitis-like variant in an ulcerative colitis patient. Intern Med 2002; 41:1013–1015
61 Casey MB, Tazelaar HD, Myers JL, et al. Noninfectious lung pathology in patients with Crohn's disease. Am J Surg Pathol 2003; 27:213–219
62 Davies D, MacFarlane A. Fibrosing alveolitis and treatment with sulphasalazine. Gut 1974; 15:185–188
63 McCulloch AJ, McEvoy A, Jackson JD, et al. Severe steroid responsive pneumonitis associated with pyoderma gangrenosum and ulcerative colitis. Thorax 1985; 40:314–315
64 Teague WG, Sutphen JL, Fechner RE. Desquamative interstitial pneumonitis complicating inflammatory bowel disease of childhood. J Pediatr Gastroenterol Nutr 1985; 4:663–667
65 Swinburn CR, Jackson GJ, Cobden I, et al. Bronchiolitis obliterans organising pneumonia in a patient with ulcerative colitis. Thorax 1988; 43:735–736
66 Balestra DJ, Balestra ST, Wasson JH. Ulcerative colitis and steroid-responsive, diffuse interstitial lung disease: a trial of N = 1. JAMA 1988; 260:62–64
67 Puntis JW, Tarlow MJ, Raafat F, et al. Crohn's disease of the lung. Arch Dis Child 1990; 65:1270–1271
68 Hotermans G, Benard A, Guenanen H, et al. Nongranulomatous interstitial lung disease in Crohn's disease. Eur Respir J 1996; 9:380–382
69 Mahajan L, Kay M, Wyllie R, et al. Ulcerative colitis presenting with bronchiolitis obliterans organizing pneumonia in a pediatric patient. Am J Gastroenterol 1997; 92:2123–2124
70 Singh R, Sundaram P, Joshi JM. Upper lobe fibrosis in ulcerative colitis. J Assoc Phys India 2003; 51:515–517
71 Sanjeevi A, Roy HK. Necrobiotic nodules: a rare pulmonary manifestation of Crohn's disease. Am J Gastroenterol 2003; 98:941–943
72 Golpe R, Mateos A, Perez-Valcarcel J, et al. Multiple pulmonary nodules in a patient with Crohn's disease. Respiration 2003; 70:306–309
73 Isenberg JI, Goldstein H, Korn AR, et al. Pulmonary vasculitis: an uncommon complication of ulcerative colitis; report of a case. N Engl J Med 1968; 279:1376–1377
74 Stebbing J, Askin F, Fishman E, et al. Pulmonary manifestations of ulcerative colitis mimicking Wegener's granulomatosis. J Rheumatol 1999; 26:1617–1621
75 Faller M, Gasser B, Massard G, et al. Pulmonary migratory infiltrates and pachypleuritis in a patient with Crohn's disease. Respiration 2000; 67:459–463
76 Krishnan S, Banquet A, Newman L, et al. Lung lesions in children with Crohn's disease presenting as nonresolving pneumonias and response to infliximab therapy. Pediatrics 2006; 117:1440–1443
77 Wasserman F, Krosnick A, Tumen H. Necrotizing angiitis associated with chronic ulcerative colitis. Am J Med 1954; 17:736–743

78 Forrest JA, Shearman DJ. Pulmonary vasculitis and ulcerative colitis. Am J Dig Dis 1975; 20:482–486
79 Collins WJ, Bendig DW, Taylor WF. Pulmonary vasculitis complicating childhood ulcerative colitis. Gastroenterology 1979; 77:1091–1093
80 Sargent D, Sessions JT, Fairman RP. Pulmonary vasculitis complicating ulcerative colitis. South Med J 1985; 78:624–625
81 Prekates AA, Orfanos SE, Routsi CJ, et al. Churg-Strauss syndrome occurring 30 years after the onset of ulcerative colitis. Respir Care 2002; 47:167–170
82 Patwardhan RV, Heilpern RJ, Brewster AC, et al. Pleuropericarditis: an extraintestinal complication of inflammatory bowel disease; report of three cases and review of literature. Arch Intern Med 1983; 143:94–96
83 Thompson DG, Lennard-Jones JE, Swarbrick ET, et al. Pericarditis and inflammatory bowel disease. Q J Med 1979; 48:93–97
84 Mukhopadhyay D, Nasr K, Grossman BJ, et al. Pericarditis associated with inflammatory bowel disease. JAMA 1970; 211:1540–1542
85 Abid MA, Gitlin N. Pericarditis: an extraintestinal complication of inflammatory bowel disease. West J Med 1990; 153:314–315
86 Rheingold OJ. Inflammatory bowel disease and pericarditis [letter]. Ann Intern Med 1975; 82:592
87 Mowat NA, Bennett PN, Finlayson JK, et al. Myopericarditis complicating ulcerative colitis. Br Heart J 1974; 36:724–727
88 Camus P, Colby TV. The lung in inflammatory bowel disease. Eur Respir J 2000; 15:5–10
89 D'Arienzo A, Manguso F, Scarpa R, et al. Ulcerative colitis, seronegative spondyloarthropathies and allergic diseases: the search for a link. Scand J Gastroenterol 2002; 37:1156–1163
90 Myrelid P, Dufmats M, Lilja I, et al. Atopic manifestations are more common in patients with Crohn disease than in the general population. Scand J Gastroenterol 2004; 39:731–736
91 Persson PG, Bernell O, Leijonmarck CE, et al. Survival and cause-specific mortality in inflammatory bowel disease: a population-based cohort study. Gastroenterology 1996; 110:1339–1345
92 Kanazawa H, Yoshikawa J. A case-control study of bronchial asthma associated with ulcerative colitis: role of airway microvascular permeability. Clin Exp Allergy 2005; 35:1432–1436
93 Storch I, Sachar D, Katz S. Pulmonary manifestations of inflammatory bowel disease. Inflamm Bowel Dis 2003; 9:104–115
94 Omori H, Asahi H, Inoue Y, et al. Pulmonary involvement in Crohn's disease: report of a case and review of the literature. Inflamm Bowel Dis 2004; 10:129–134
95 Vaiphei K, Gupta N, Sinha SK, et al. Association of ulcerative colitis with pulmonary sarcoidosis, subcutaneous lipomatosis and appendiceal adenocarcinoma. Indian J Gastroenterol 2003; 22:193–194
96 Brunin G, Rohart P, Aron C. Sarcoidosis in a patient with Crohn disease [in French]. Rev Pneumol Clin 1997; 53:347–349
97 Cox NH, McCrea JD. A case of Sjogren's syndrome, sarcoidosis, previous ulcerative colitis and gastric autoantibodies. Br J Dermatol 1996; 134:1138–1140
98 Van Steenbergen W, Fevery J, Vandenbrande P, et al. Ulcerative colitis, primary sclerosing cholangitis, bile duct carcinoma, and generalized sarcoidosis: report of a unique association. J Clin Gastroenterol 1987; 9:574–579
99 Barr GD, Shale DJ, Jewell DP. Ulcerative colitis and sarcoidosis. Postgrad Med J 1986; 62:341–345
100 Papadopoulos KI, Hornblad Y, Liljebladh H, et al. High frequency of endocrine autoimmunity in patients with sarcoidosis. Eur J Endocrinol 1996; 134:331–336
101 Storch I, Rosoff L, Katz S. Sarcoidosis and inflammatory bowel disease. J Clin Gastroenterol 2001; 33:345
102 Letizia C, D'Ambrosio C, Agostini D, et al. Serum angiotensin converting enzyme activity in Crohn's disease and ulcerative colitis. Ital J Gastroenterol 1993; 25:23–25
103 Lewis M, Kallenbach J, Zaltzman M, et al. Severe deficiency of $\alpha_1$-antitrypsin associated with cutaneous vasculitis, rapidly progressive glomerulonephritis, and colitis. Am J Med 1985; 79:489–494
104 Taddei C, Audrain MA, Reumaux D, et al. $\alpha_1$-Antitrypsin phenotypes and anti-neutrophil cytoplasmic auto-antibodies in inflammatory bowel disease. Eur J Gastroenterol Hepatol 1999; 11:1293–1298
105 Elzouki AN, Eriksson S, Lofberg R, et al. The prevalence and clinical significance of $\alpha_1$-antitrypsin deficiency (PiZ) and ANCA specificities (proteinase 3, BPI) in patients with ulcerative colitis. Inflamm Bowel Dis 1999; 5:246–252
106 Folwaczny C, Urban S, Schroder M, et al. $\alpha_1$-Antitrypsin alleles and phenotypes in patients with inflammatory bowel disease. Scand J Gastroenterol 1998; 33:78–81
107 Yang P, Tremaine WJ, Meyer RL, et al. $\alpha_1$-Antitrypsin deficiency and inflammatory bowel diseases. Mayo Clin Proc 2000; 75:450–455
108 Talbot RW, Heppell J, Dozois RR, et al. Vascular complications of inflammatory bowel disease. Mayo Clin Proc 1986; 61:140–145
109 Quera R, Shanahan F. Thromboembolism: an important manifestation of inflammatory bowel disease. Am J Gastroenterol 2004; 99:1971–1973
110 Papa A, Danese S, Grillo A, et al. Review article: inherited thrombophilia in inflammatory bowel disease. Am J Gastroenterol 2003; 98:1247–1251
111 Oldenburg B, Fijnheer R, van der Griend R, et al. Homocysteine in inflammatory bowel disease: a risk factor for thromboembolic complications? Am J Gastroenterol 2000; 95:2825–2830
112 Solem CA, Loftus EV, Tremaine WJ, et al. Venous thromboembolism in inflammatory bowel disease. Am J Gastroenterol 2004; 99:97–101
113 Novacek G, Miehsler W, Kapiotis S, et al. Thromboembolism and resistance to activated protein C in patients with inflammatory bowel disease. Am J Gastroenterol 1999; 94:685–690