

## Respiratory Involvement in Children with Inflammatory Bowel Disease

Guy Gut, M.D., and Yakov Sivan, M.D.

Inflammatory bowel diseases (IBDs), including Crohn's disease and ulcerative colitis, are systemic diseases with a variety of extra-intestinal manifestations. Respiratory involvement, whether clinically symptomatic or latent, may be more common than previously thought. As opposed to adults, most of the cases in children involve Crohn's disease. The pathogenesises of the pulmonary manifestations are obscure. The inflammatory process is not restricted to the bowel as has been suggested by findings of high levels of fractional exhaled nitric oxide (FeNO) in the airways. Increased FeNO has been reported even during clinical remission, while increasing further during exacerbations. Pulmonary manifestations develop usually after the onset of the bowel disease; however, they may emerge after colectomy and cessation of therapy. Pulmonary lesions in children usually involve the lung parenchyma with granulomatous infiltrates. Other less common injuries involve the airways and the pleura. The most prevalent pathologies in adults are bronchiectasis, cryptogenic organizing pneumonia, and small airway disease. Pulmonary involvement in IBD is often latent or sub-clinical and may be detected solely by laboratory or imaging techniques. Abnormalities in pulmonary function tests (PFTs) are not consistent except for low-diffusion capacity for carbon monoxide, which was found in both children and adults. High-resolution computed tomography (CT) is a sensitive tool for detecting lung involvement and may reveal abnormalities even when PFTs are normal and the patient is asymptomatic. Medications used for IBD, especially nonsteroidal anti-inflammatory drugs, are also a risk factor for lung injury. Treatment of pulmonary involvement often includes systemic corticosteroids with subsequent prolonged treatment of inhaled steroids in appropriate selected cases. Other immune-modulators have been tried. Pediatricians, especially those treating children with IBD, pediatric gastroenterologists, and pediatric pulmonologists should have a high index of suspicion and be aware of tools to be used in the assessment and treatment of pulmonary complications in IBD.

### Key Points Box

What does this review show for respiratory involvement in children with inflammatory bowel disease (IBD)?

1. Respiratory involvement in IBD is not very rare.
2. Pulmonary involvement may be asymptomatic and present only as radiologic and physiologic derangements.
3. Most children with respiratory involvement have Crohn's disease.
4. Pulmonary involvement may start or worsen following bowel surgery.
5. Exhaled nitric oxide is elevated during remission with further increase during exacerbation.
6. High-resolution computed tomography is a sensitive tool for detecting lung involvement.
7. Pulmonary function tests may exhibit a variety of changes.
8. Treatment options include steroids and other immune modulator drugs such as antitumor necrosis factor  $\alpha$  antibodies in addition to supportive treatment.

### Case Report

A 15-YEAR-OLD GIRL STARTED to cough after a sub-total colectomy for ulcerative colitis that was resistant to treatment. Her medical history was uneventful except for atopic dermatitis. There was no history of respiratory disease. Family history was unremarkable. At the age of 14 years she was found to have ulcerative colitis and pancolitis. She was treated with sulfasalazine (5-aminosalicylic acid [5-ASA] with sulfapyridine), 6 mercaptopurine (6MP), oral corticosteroids, and the tumor necrosis factor  $\alpha$  (TNF- $\alpha$ ) inhibitor infliximab. Nevertheless, she suffered many exacerbations and required repeated hospitalizations due to an uncontrolled disease. Subsequently, she underwent sub-total colectomy. Her perioperative course was normal. Treatment with corticosteroids and 6MP was gradually tapered off without recurrence of the gastrointestinal symptoms. Within a week after the surgery, she started with productive cough that did not respond to inhaled bronchodilators and steroids. Wheezing and coarse crackles were heard over the

right lower lung field. Chest radiograph showed mild bilateral hyperinflation with bronchial thickening at the right lower lobe (RLL). Laboratory work-up revealed normal complete blood count (CBC) and chemistry with mild elevation of C-reactive protein. Sweat test and tuberculin skin test purified protein derivative (PPD) were negative. Spirometry showed forced expiratory flow in 1 minute (FEV<sub>1</sub>)=61%, FEV<sub>1</sub>/forced vital capacity (FVC)=90%, and FEF<sub>75-25</sub>=41% (percent of predicted values) without improvement after bronchodilators. Fractional exhaled nitric oxide (FeNO) was elevated to 78 ppb (normal levels at our laboratory <23 ppb). Chest CT scan, performed 3 months after colectomy, showed diffuse bronchiectasis involving all lung fields. Flexible bronchoscopy revealed normal anatomy without signs of inflammation. Bronchoalveolar lavage showed moderate neutrophilia with normal CD4/CD8 ratio. Her productive cough worsened, she became moribund, could not attend school, and was confined to a wheel chair. Treatment with macrolides, high-dose inhaled steroids (Budesonide 800 mcg/day), bronchodilators, and physical therapy achieved gradual but consistent improvement. Systemic steroids were reserved for exacerbations and preoperatively (ileal pouch anal anastomosis). Over the next 6 months, cough became minimal and she resumed full school and physical activities. Chest auscultation still reveals mild diffuse crackles. However, all medications have been discontinued without any further exacerbations of her gastrointestinal or lung diseases.

### Respiratory Involvement in Children with Inflammatory Bowel Disease: Background

Inflammatory bowel diseases (IBDs) include Crohn's disease and ulcerative colitis, 2 chronic inflammatory diseases of the gastrointestinal tract that are characterized by exacerbations and remissions. Although these 2 entities differ in several aspects, including pathogenesis, intestinal involvement, symptoms, and treatment, a variety of extra-intestinal manifestations frequently occur in both.<sup>1-3</sup> The most common organs involved are the eyes, skin, joints, and the liver. Dotson et al. showed an incidence of 28% of extra-intestinal involvement in 1,009 children with IBD with differences in the prevalence of specific complications between Crohn's disease and ulcerative colitis.<sup>4</sup> Respiratory involvement was first suggested by Kraft et al. in 1976. They reported 6 cases of respiratory morbidity in Crohn's disease and ulcerative colitis.<sup>5</sup> Accumulating reports now suggest that what was once believed to be a rare complication of IBD is now being recognized more frequently.<sup>6-9</sup> However, notwithstanding the number of reports linking lung disease and IBD, this association is often overlooked in children, especially because most case reports involve adults and very few reports in children (Table 1).

### Epidemiology

The true prevalence of pulmonary complications in IBD remains unknown. Two issues make the conclusion of prevalence difficult: the findings that respiratory involvement may be sub-clinically and such abnormalities may either resolve or persist during bowel remission. One study reported an incidence of asthma in up to 20% of subjects.<sup>10</sup> Respiratory complications may not be infrequent when

both clinical and subclinical (radiologic or lung function abnormalities during active bowel disease or during bowel remissions) are considered.<sup>6-8</sup> Respiratory symptoms have been reported in up to 25%–50% of IBD adult subjects in case series of 30 to 40 cases.<sup>11-14</sup> True prevalence in children is unknown since pediatric reports of respiratory involvement are scarce. Two large pediatric studies involving >2,600 cases that evaluated extra-intestinal manifestations in IBD did not indicate any respiratory involvement.<sup>4,15</sup> This may, however, be due to lack of awareness. Table 1 summarizes the case reports published in children.<sup>16-28</sup> These reports showed an almost equal occurrence in males and females. Subjects were generally in their 2nd decade of life and most of the cases suffered from Crohn's disease. Unpublished personal data from Philippe Camus regarding the international registry of respiratory involvement in IBD confirm that only few pediatric cases have so far been reported.

### Pathogenesis

Pathogenetic mechanisms for pulmonary involvement in IBD are unknown. Both the colon and the bronchial tree are derived from the primitive gut and have columnar epithelia with goblet cells, submucosal mucus glands, and lymphoid tissue. One explanation relies upon the "shared antigen theory." The permeable intestinal barrier is penetrated by products that cross-react with shared antigens in the human body.<sup>29</sup> Another theory suggests that circulating immune complexes and complement deposition are responsible for pulmonary flare-ups.<sup>30</sup> Yet, the pathogenesis of IBD and of many of the reported pulmonary diseases associated with it remains vague.

The timing of the pulmonary involvement is not consistent. In >50% (8 of 15) of the pediatric cases, the respiratory involvement followed the IBD, whereas in 3 of them it precedes it, and 4 cases presented with colonic and lung disease at the same time (Table 1). In most adult cases, pulmonary manifestations develop after the onset of the bowel disease.<sup>6</sup> An intriguing observation is that in some reports of adults with IBD, mostly ulcerative colitis, and in 1 pediatric case, respiratory involvement was described after colonic surgery and in some cases worsened in the days to months after such surgery.<sup>25,31-35</sup> Our patient also presented similarly. In 8 out of 10 adults with IBD (5 with ulcerative colitis) and bronchiectasis, described by Kelly and colleagues, the onset of respiratory symptoms followed colectomy.<sup>33</sup> The mechanism for this phenomenon remains obscure. Some believe that the withdrawal of the immune suppression treatment after colectomy enables the inflammatory process to accelerate. Another theory suggests that the surgical procedure is responsible for the development of respiratory symptoms and disease. Regardless of mechanism, the possibility that colectomy could precipitate pulmonary complications in IBD patients should be kept in mind.

Infections complicating IBD are a logical theory that may explain respiratory involvement. However, all the case reports in children and the large reviews available in adults presented negative results after a thorough and aggressive work-up for infection that included search for bacterial, viral, and opportunistic pathogens in blood, saliva, bronchoalveolar lavage, and tissue biopsies. Serologic tests were also uninformative. Special attention was paid to rule out

mycobacterium infection and in some of the cases treatment was initiated until negative culture results.<sup>27</sup> Camus described occasional growth of *Candida albicans* and *Hemophilus influenza* with questionable clinical relevance.<sup>9</sup>

## Inflammation

Increased production of nitric oxide has been demonstrated in IBD, mainly in ulcerative colitis.<sup>36</sup> Nitric oxide levels were found to be increased 100-fold in aspirated colonic and rectal gas of ulcerative colitis patients.<sup>37,38</sup> An observation in adults is the increased FeNO in the airways of IBD patients. Koek et al. found a positive correlation between the degree of the intestinal disease and levels of FeNO.<sup>39</sup> A recent study from Turkey showed significantly higher FeNO levels in IBD patients with pulmonary involvement compared with IBD patients without pulmonary involvement and normal controls (32, 24, and 14 ppb, respectively). Sensitivity and specificity analysis with receiver operator characteristic curve analysis failed to present a reliable cutoff value for FeNO as a marker for the pulmonary involvement probably due to a small study population (33 IBD, 15/33 with pulmonary involvement).<sup>40</sup> This, nevertheless, supports the assumption that pulmonary involvement in IBD is associated with inflammation. Preliminary findings from our lab show higher levels of FeNO also in children with IBD during remission compared with healthy controls, suggesting that FeNO may be used as a screening to identify patients with pulmonary involvement. It is yet to be defined whether FeNO levels may be used as a simple noninvasive tool to identify also intestinal flare-up.

Several explanations have been proposed for the increased FeNO in IBD. An interesting theory is that the inflammatory process is not restricted to the bowel. Inflammatory cells that migrate to other sites through the systemic circulation are responsible for the extra-intestinal manifestations. Indeed, activated lymphocyte accumulations have been reported in bronchoalveolar lavage and induced sputum samples in asymptomatic patients with IBD.<sup>41</sup> Thus, FeNO may reflect lung co-inflammation.

## Pulmonary Manifestations of IBD

### Symptoms

Symptoms in pediatric and adult patients usually are non-specific and include cough, wheeze, sputum production, dyspnea, stridor, and hoarseness. Weight loss was reported in children. Physical examination is frequently normal. Inspiratory crackles and diminished respiratory sounds may be observed.<sup>7,9</sup> However, sub-clinical radiologic and laboratory involvement does exist (see below). It is useful to classify pulmonary involvement in IBD according to its anatomical site.

### Parenchymal Involvement

The most common site of respiratory involvement in children is parenchymal, whether alveolar or interstitial. In almost half of the pediatric cases biopsy showed noncaseating granulomas with giant cells.<sup>16,18–22</sup> All of them had Crohn's disease, which had been diagnosed several years before the respiratory symptoms emerged. Two pediatric cases of ulcerative colitis with respiratory involvement exhibited interstitial lung disease<sup>17,23</sup> and a third suffered from interstitial and airway disease.<sup>24</sup> It is important to emphasize

that any discussion regarding interstitial lung disease in IBD should consider the exposure to bowel disease-modifying drugs like the salazines. Indeed, some of the children developed the lung disease while on IBD drugs such as 5-ASA, 6MP, and corticosteroids. Cryptogenic organizing pneumonia, previously termed as idiopathic bronchiolitis obliterans organizing pneumonia (BOOP), is the most commonly reported parenchymal manifestation of IBD in adults<sup>9,42</sup> with 21 out of 40 cases in 1 series.<sup>7</sup> This was also reported in a couple of pediatric cases.<sup>16,19</sup> Symptoms may include fever and dyspnea. Other patterns of injury, reported mainly in adults, included interstitial fibrosis, pneumonitis, and sterile necrotic nodules.<sup>43–46</sup> Parenchymal involvement may necessitate lung biopsy for diagnosis and to guide treatment.

### Airway Disease

There are only 2 case reports of airway involvement in pediatric IBD patients. One described a 13-year-old girl with interstitial lung disease and developed necrotizing bronchiolitis and bronchiectasis later in the course of the disease.<sup>24</sup> The second described a boy who developed respiratory symptoms early in the first months of life and was found to have Crohn's disease with bronchiectasis later.<sup>21</sup> In comparison, in adults with IBD, airway involvement is much more common. Black et al. reviewed 55 studies including 155 patients with respiratory involvement, most of whom had ulcerative colitis and all of whom were adults.<sup>7</sup> They found large airways involvement in 39% of the cases, 2/3 of them presented with bronchiectasis. The mean age was around 40 years with small airway disease presenting at younger age. It is tempting to suggest that immune suppression by IBD medication is responsible for recurrent pulmonary infections that eventually cause bronchiectasis. That in previous reports and in our case bronchiectasis was the first presentation of respiratory involvement without evidence of prior respiratory morbidity undermines this theory.

Large airway patterns of injury include acute (rare) and chronic (more common) bronchitis and suppurative large airway disease.<sup>6,9,31,47–49</sup> Small airway disease is less common. Its occurrence in Crohn's disease and ulcerative colitis is similar,<sup>7</sup> and it may take the pattern of diffuse bronchiolitis, granulomatous bronchiolitis,<sup>50</sup> or bronchiolitis obliterans.<sup>51</sup>

A rare type of airway disease associated with IBD in adults is upper airways obstruction due to inflammation and fibrosis which almost always involves the trachea.<sup>52,53</sup>

### Serositis

Pleural effusions were reported in 2 pediatric cases—both of them were boys with Crohn's disease and parenchymal lung disease.<sup>16,18</sup> There are a few reports of this complication in adults as well.<sup>54–56</sup>

### Other Manifestations

Thromboembolic events and other rare pulmonary manifestations associated with IBD have been described mainly in adults.<sup>57</sup> One 16-year-old adolescent who suffered from pulmonary embolism 3 years after being found to have Crohn's disease was reported by Krishnan et al. He was treated with low-molecular-weight heparin (enoxaparin) and later developed cryptogenic organizing pneumonia.<sup>16</sup> A

TABLE 1. SUMMARY OF REPORTED CASES OF RESPIRATORY INVOLVEMENT IN CHILDREN WITH INFLAMMATORY BOWEL DISEASE (REVIEW OF THE LITERATURE)

| <i>Study reference</i>          | <i>IBD type</i> | <i>Sex</i> | <i>Age</i> | <i>Tx. at presentation</i> | <i>Description</i>                                                                                                                                                                                                                                                                                   | <i>Tx.</i>                        | <i>Respiratory outcome</i>    |
|---------------------------------|-----------------|------------|------------|----------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------|-------------------------------|
| Krishnan et al. <sup>16</sup>   | CD              | F          | 13         | Prednisone + 6MP           | 3 years after diagnosis, fever cough, hypoxemia. CT—nodules. PFT—restrictive. Lung biopsy—noncaseating granulomas with giant cells                                                                                                                                                                   | Infliximab                        | Respiratory symptoms free     |
|                                 | CD              | M          | 17         | Mesalamine + 6MP           | 4 years after diagnosis of CD, PE at 16 years. presented at age 17 with fever, chest pain, aphtous. CXR—bilateral. Pleural effusion. Biopsy—BOOP                                                                                                                                                     | Infliximab                        | Respiratory symptoms free     |
|                                 | CD              | F          | 14         | Mesalamine                 | 3 years after diagnosis of CD, EIA. Presented with chest tightness, shortness of breath, cough. CXR—Left infiltrate. CT—multiple granulomatous lesions. Biopsy—noncaseating granulomas with giant cells.                                                                                             | Infliximab                        | Complete resolution           |
| Carvalho et al. <sup>17</sup>   | UC              | F          | 13.5       |                            | 2 years after diagnosis, no respiratory symptoms. CT—nodules. PFT—obstructive. Biopsy—alveolar inflammation.                                                                                                                                                                                         | Steroids mesalamine 6MP           |                               |
| Puntis et al. <sup>18</sup>     | CD              | M          | 17         | Mesalamine                 | 2 years after diagnosis, fever and chest pain. CXR—Left infiltrate + pleural effusion. Biopsy—noncaseating granulomas with giant cells.                                                                                                                                                              |                                   |                               |
| Levenbrown et al. <sup>19</sup> | CD              | F          | 15         |                            | Night sweat and weight loss for 6 months. Cough and recurrent pneumonias. CT—nodules. Biopsy—noncaseating granulomas with giant cells + COP. Colonoscopy revealed the diagnosis of CD.                                                                                                               | Steroids mesalamine methotrexate  |                               |
| Bentur et al. <sup>20</sup>     | CD              | F          | 13         | Sulfasalazine prednisone   | 10 months after diagnosis, exercise intolerance, dyspnea, clubbing, cyanosis. CXR—normal. HRCT—mosaic with patches of ground glass appearance. PFT—restrictive and obstructive. DLCO = 70%. Biopsy—noncaseating granulomas and BO. Stopped sulfasalazine and started mesalamine without improvement. | 6-MP steroids Hydroxy-chloroquine | Respiratory symptoms improved |
| Akobeng et al. <sup>21</sup>    | CD              | M          | 9          |                            | Persistent lobar atelectasis and consolidation from infancy, lobectomy at 4 years. Chronic diarrhea with FTT. Later on developed bronchiectasis. Diagnosed with CD at 9 years.                                                                                                                       | Intermittent oral steroids        |                               |

(continued)

TABLE 1. (CONTINUED)

| <i>Study reference</i>         | <i>IBD type</i> | <i>Sex</i> | <i>Age</i> | <i>Tx. at presentation</i> | <i>Description</i>                                                                                                                                                                                                                                                                                                                                                                                              | <i>Tx.</i>                                   | <i>Respiratory outcome</i>                     |
|--------------------------------|-----------------|------------|------------|----------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------|------------------------------------------------|
| Calder et al. <sup>22</sup>    | CD              | M          | 3          |                            | Presented with swollen gums and perianal soreness. CXR—right field infiltrates. Biopsy (lung, gums, and anal skin tag)—noncaseating granulomas with giant cells.                                                                                                                                                                                                                                                |                                              |                                                |
| Teague et al. <sup>23</sup>    | UC              | M          | 13         | Sulfasalazine              | 5 years after diagnosis, exercise intolerance, clubbing, inspiratory rales. CXR—interstitial infiltrates. Biopsy-DIP with eosinophilia. Liver biopsy—cirrhosis.                                                                                                                                                                                                                                                 | Prednisone azathioprine                      | Died 2 years after onset of pulmonary symptoms |
| Mazer et al. <sup>24</sup>     | UC              | F          | 13         |                            | 2 year history of steroid dependent ILD. CXR-diffuse interstitial infiltrates. PFT—restrictive, DLCO = 36%. Biopsy—bronchiectasis with interstitial pneumonitis. Developed GI signs and was diagnosed with UC.                                                                                                                                                                                                  | Sulfasalazine with tapering off the steroids | Respiratory symptoms free                      |
| Kayser et al. <sup>25</sup>    | CD              | M          | 12         |                            | 3 years after diagnosis and after ileal resection presented with tachypnea and dyspnea. Biopsy—granulomatous interstitial lymphocyte infiltrates and acute alveolitis.                                                                                                                                                                                                                                          | Prednisone azathioprine                      | Respiratory symptoms free                      |
| Al-Binali et al. <sup>26</sup> | CD              | M          | 11         |                            | Nonresolving pneumonia, cough exercise intolerance. Eight months later suffered from diarrhea and abdominal pain. Clubbing, fine inspiratory crackles. Oral aphthous ulcer and anal fissures. CXR—patchy air-space consolidation. CT—multiple peripheral nodules. PFT-restrictive. DLCO = 44%. Biopsy—noncaseating granulomas. GIT endoscopy—widespread inflammation with multiple ulcers throughout the colon. | Refuse treatment                             | Respiratory symptoms free                      |
| Minic et al. <sup>27</sup>     | CD              | F          | 15         |                            | Presented with concomitantly respiratory and GI symptoms. Late inspiratory crackles, clubbing; CXR—RML infiltrate. PFT + DLCO—normal. BAL—lymphocytosis. Biopsy noncaseating and epithelioid granulomas.                                                                                                                                                                                                        | Prednisone sulphasalazine                    | Respiratory symptoms free                      |
| Le Roux et al. <sup>28</sup>   | CD              | F          | 13         |                            | 1.5 years after diagnosis. Exercise intolerance. BAL—lymphocytosis. Biopsy—normal.                                                                                                                                                                                                                                                                                                                              |                                              |                                                |

<sup>6</sup>MP, 6 mercaptopurine; BAL, bronchoalveolar lavage; BOOP, bronchiolitis obliterans organizing pneumonia; CD, Crohn's disease; COP, cryptogenic organizing pneumonia; CT, computed tomography; CXR, chest X-ray; DIP, desquamative interstitial pneumonia; DLCO, diffusion capacity of the lung for carbon monoxide; ELA, exercise-induced asthma; FTT, failure to thrive; GIT, gastrointestinal tract; IBD, inflammatory bowel disease; ILD, interstitial lung disease; PE, pulmonary embolism; PFT, pulmonary function test; UC, ulcerative colitis.

recent large Danish study observed an increased risk for deep vein thrombosis and pulmonary embolism in both children and adults.<sup>58</sup> Rare occurrence of  $\alpha$ 1-antitrypsin deficiency was reported mainly in adults with ulcerative colitis.<sup>59–61</sup> Sarcoidosis was concomitantly reported with Crohn's disease in >40 adult cases<sup>29</sup> and is suggested as a differential diagnosis almost in every case of Crohn's disease and pulmonary involvement due to the pathologic resemblance. Recurrent or antibiotic-resistant left lower lobe pneumonias in patients with Crohn's disease should raise the suspicion of a colobronchial fistulae.<sup>62,63</sup>

## Pulmonary Functions

Abnormalities in pulmonary functions have been found in children with both Crohn's disease and ulcerative colitis, including changes in maximal flow rates, lung volumes, and mainly in diffusion capacity. Munck et al. performed pulmonary function test (PFT) in 26 children with Crohn's disease, all of them without respiratory symptoms and with normal chest radiographs. They did not find any difference in spirometry and lung volumes in patients with active disease compared with those in remission. Except for 3 children with active disease who showed restrictive pattern, all others had normal indices.<sup>64</sup> In the pediatric reports mentioned above, restrictive, obstructive, and mixed patterns were noticed<sup>16–20,24,26</sup> (Table 1). In the adult group, Tzanakis et al.<sup>65</sup> studied PFTs in 132 IBD patients (47 with Crohn's disease and 85 with ulcerative colitis) and found no significant differences in spirometric indices between patients and healthy controls. Herrlinger et al. showed decreased FEV<sub>1</sub> in both ulcerative colitis and Crohn's disease adult patients at remission compared with healthy controls. FEV<sub>1</sub> was further decreased during active disease.<sup>66</sup> Mohamed-Hussein et al.<sup>67</sup> detected PFT abnormalities in 15 of 26 (57%) adult ulcerative colitis patients. The most common was a decrease in FEF<sub>75–25</sub>, followed by reduced FEV<sub>1</sub>. These changes correlated with disease activity. These findings were supported also by recent publications.<sup>14,68</sup> Findings in patients with disease onset in childhood were no different from those with disease onset as adults.<sup>66</sup> Air entrapment with increased functional residual capacity (FRC) and increased residual volume to FRC ratio (residual volume [RV]/FRC) was also observed in adults.<sup>12,69</sup>

Challenge testing for bronchial hyper-responsiveness has been reported in patients with IBD. Mansi et al. performed methacholine provocation tests in 14 children with Crohn's disease without clinical airway disease. The mean age was 12 years. The rate of hyper-responsiveness was 71% compared with 100% in asthmatic children and 0% in healthy controls.<sup>70</sup> There was no relation to disease activity or treatment. Similarly, high rates of bronchial hyper-responsiveness have also been reported in adults.<sup>71</sup>

The most repeatable abnormality of lung function in IBD patients is the decrease in diffusion capacity of the lung for carbon monoxide (DLCO) observed in both Crohn's disease and ulcerative colitis. In the 26 children studied by Munck et al., a decrease in DLCO was observed during active disease compared with remission.<sup>64</sup> While several studies in adults found that it correlated with disease activity with a decrease in diffusion capacity during exacerbations of bowel disease,<sup>12,65,72,73</sup> others found similar reduction in

DLCO not only during an active disease but also during remission.<sup>11,74,75</sup> The reduction in DLCO could indicate an alveolitis or alveolar-capillary dysfunction, which may be related to the increased capacity of alveolar macrophages to produce superoxide anions, as reported in Crohn's disease.<sup>76</sup> Histopathological studies are needed to better explain this phenomena.

## Radiology

Chest radiography is usually normal in patients with IBD and can stay normal despite of pulmonary involvement.<sup>9,40,77</sup> Nevertheless, pulmonary infiltrates, either alveolar or interstitial, were found in children with lung involvement.<sup>16,18,21,22</sup> Findings on CT scans include pulmonary abnormalities, but most reports did not correlate CT findings with clinical and pulmonary function data. One study that did investigate these relationships was performed by Mahadeva et al.<sup>35</sup> in 17 adults with IBD (14 with ulcerative colitis), all during inactive bowel disease. Bronchiectasis was found in 13/17 patients (11/14 ulcerative colitis and 2/3 Crohn's disease), 11 had air trapping, and 5 had a "tree in bud" appearance. However, 6 of the 13 patients with bronchiectasis had normal PFTs. Another study (*n*=52) found pulmonary abnormalities in CT in 50% and 60% of ulcerative colitis and Crohn's disease adult patients, respectively.<sup>78</sup> Similar results were reported also by Songur et al.<sup>12</sup> and Yilmaz et al.<sup>14</sup> with the CT abnormalities being air-trapping, peribronchial thickness, ground-glass opacifications, peripheral reticular opacities, and cysts. A recent study that showed pulmonary involvement in 15 of 33 (45%) adult patients with IBD (25 ulcerative colitis and 8 Crohn's disease) also found that CT was the most sensitive test for pulmonary involvement.<sup>40</sup> Out of the 15 cases, pulmonary abnormalities were diagnosed in 13 using high resolution computerized tomography (HRCT) and in only 2 by PFTs and DLCO. Hence, radiologic evidence of pulmonary involvement in IBD may be the only abnormality and occur without clinical or even physiologic derangements. CT may be required for early diagnosis of parenchymal involvement. However, its clinical significance is unclear.

## Asthma and Allergic Disorders

The association between atopy and IBD is not new.<sup>79</sup> Bernstein et al. found increased prevalence and a more severe course of asthma among adult IBD patients compared with healthy subjects.<sup>10</sup> This was supported also by Raj et al. for ulcerative colitis who reported a 4 times higher prevalence of IBD among patients with airway disease, like COPD, chronic bronchitis, and bronchiectasis compared with the general population.<sup>80</sup> The increased occurrence of Crohn's disease in asthmatics did not reach a statistical significance. Other studies have shown increased rates of atopic features, history of atopy, positive skin prick, and high IgE levels in adult IBD patients.<sup>13,81–84</sup> Sputum eosinophilia was observed by Fireman et al. in adults with ulcerative colitis.<sup>85</sup>

## Drug-Induced Lung Disease

Special attention must be paid to respiratory adverse drug reactions from the variety of treatments for IBD. The 2 drugs

linked the most to pulmonary adverse effects are mesalamine—a 5-ASA—and sulfasalazine (a combination of 5-ASA and sulfapyridine), both used frequently in the treatment of ulcerative colitis and Crohn's disease. Side effects of sulfasalazine and mesalamine may be dose related or idiosyncratic. Like aspirin, both compounds can cause cough and exacerbation of underlying asthma. The most commonly described abnormalities due to sulfasalazine therapy are eosinophilic pneumonia, interstitial pneumonitis, BOOP, and cavitating nodules.<sup>86</sup> From the 15 pediatric case reports (Table 1), in 5 the respiratory symptoms occurred while under treatment with one of these drugs. At least in 3 of them, changing to other immune suppression strategy achieved respiratory improvement.<sup>16,18,20</sup> A review of the literature for sulphasalazine lung toxicity by Parry and colleagues found 50 such cases in adults.<sup>87</sup> Typical presentation included cough, fever, new onset dyspnea, hypoxemia, and infiltrates on chest radiography. Fifty percent of the cases exhibited blood eosinophilia. The most common pathology was eosinophilic pneumonitis. Drug withdrawal achieved improvement in the majority of cases with resolution within 2 months. Systemic steroids offer little or no benefit; yet, they are used frequently. There are few case reports of eosinophilic pleural effusion.

Methotrexate has been linked with pneumonitis.<sup>88</sup> Ananthakrishnan et al. described a series of IBD patients who developed severe, noninfectious pulmonary toxicity during the first month after the initiation of azathioprine or 6MP (purine analogs).<sup>89</sup> Infliximab has been associated with lung infections, mainly tuberculosis in adults.<sup>29,90</sup>

## Treatment

Treatment options for parenchymal disease comprise changing or increasing the treatment for the IBD and adding systemic steroids. Krishnan et al. described 3 adolescents suffering from Crohn's disease and severe pulmonary symptoms who did not respond to steroids and other first-line IBD treatment, but had dramatic responses to anti-TNF monoclonal antibody (Infliximab).<sup>16</sup>

In airways injury, corticosteroids, either systemic or inhaled, are the most common drugs used with good results overall.<sup>7</sup> In the study by Mahadeva et al. 11 of 17 patients exhibited a clinical or physiological response to steroids.<sup>35</sup> Camus et al. reported good results using inhaled steroids (beclomethasone or budesonide) in adult IBD patients with large and small airway disease. Systemic steroids were reserved for severe and unresponsive disease.<sup>9</sup> In some corticosteroid-resistant cases, other immunosuppressants were used.<sup>19,91</sup> Infliximab was used in 1 adult case after severe adverse reaction to steroids.<sup>92</sup>

Other measures are mainly supportive and include bronchodilation and mucus clearance strategies for airways involvement especially when bronchiectasis is present.<sup>93</sup> When the problem is drug-induced lung disease, the mainstay of treatment would be stopping the offending drug. In most of the adult cases, neither colectomy nor classic nonsteroidal IBD-modifying drugs have demonstrated any effect in controlling the respiratory manifestations of IBD.<sup>6</sup> However, in a few pediatric reports medical therapy for IBD, such as 5-ASA and other immune-modulators, achieved remission of respiratory symptoms (Table 1). As discussed earlier, colectomy can aggravate or

even trigger respiratory manifestations in adults and children with IBD.<sup>33</sup>

## Conclusions

Respiratory system involvement is an important extra-intestinal manifestation of IBD, in both Crohn's disease and ulcerative colitis. Many issues are still unclear. Histopathologic investigations in the future might shed important light on the unanswered questions related to pathogenesis in this disease. The association with Crohn's disease is more common in children. It may present with different clinical presentations with variable relationships to onset or duration of the intestinal disease. Age, type of IBD, and treatment interventions, medications, and surgery affect the occurrence of the pulmonary complications. Extrapolation from adults and preliminary data from children suggest that both airway and lung pathology may be observed in children without active bowel disease and during remission. Occasionally, abnormal laboratory and imaging findings may precede clinical presentation. The preliminary findings of increased FeNO during exacerbations require further studies to evaluate whether this test offers a tool to detect respiratory flare-up and possibly bowel exacerbation. Since asymptomatic respiratory involvement may potentially evolve into a serious disease with significant effects on quality of life, studies are needed to develop protocols to be used for screening respiratory involvement and that will be applicable and useful in the evaluation of the disease and the results of treatment. Until more data are available, we suggest that respiratory work-up be incorporated into the management routine in children with IBD. Work-up is suggested at (1) diagnosis of IBD and before treatment; (2) 2 and 4 years from diagnosis in an asymptomatic child; (3) before and 2 months after surgery (colonic). Such respiratory work-up should include: careful history of respiratory symptoms, physical examination, chest radiography, PFT including diffusion capacity, and optionally FeNO. A child presenting with respiratory symptoms at any point in the course of their IBD disease should also undergo this work-up. When airway disease is suspected and spirometry is normal, challenge tests should be considered. When parenchymal involvement is suspected and especially when bronchiectasis is considered, a HRCT is warranted. Although respiratory infections have not been found to be a common trigger for respiratory involvement in IBD, we suggest ruling out infectious causes.

Pediatricians and pediatric gastroenterologists involved in the treatment of children with IBD as well as pediatric pulmonologists who may be consulted by patients with respiratory symptoms should have a high index of suspicion and use available appropriate strategies in the assessment of these patients and during their follow-up.

## Author Disclosure Statement

None of the authors have any disclosures of financial support or conflicts of interest to declare.

## References

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

2. Greenstein AJ, Janowitz HD, Sachar DB. The extra-intestinal complications of Crohn's disease and ulcerative colitis: a study of 700 patients. *Medicine* 1976; 55:401-412.
3. Rankin GB. Extraintestinal and systemic manifestations of inflammatory bowel disease. *Med Clin North Am* 1990; 74: 39-50.
4. Dotson JL, Hyams JS, Markowitz J, LeLeiko NS, Mack DR, Evans JS, Pfefferkorn MD, Griffiths AM, Otley AR, Bousvaros A, Kugathasan S, Rosh JR, Keljo D, Carvalho RS, Tomer G, Mamula P, Kay MH, Kerzner B, Oliva-Hemker M, Langton CR, Crandall W. Extraintestinal manifestations of pediatric inflammatory bowel disease and their relation to disease type and severity. *J Pediatr Gastroenterol Nutr* 2010; 51:140-145.
5. Kraft SC, Earle RH, Roesler M, Estarly JR. Unexplained bronchopulmonary disease with inflammatory bowel disease. *Arch Intern Med* 1976; 136:454-459.
6. Camus P, Colby TV. The lung in inflammatory bowel disease. *Eur Respir J* 2000; 15:5-10.
7. Black H, Mendoza M, Murin S. Thoracic manifestations of inflammatory bowel disease. *Chest* 2007; 131:524-532.
8. Marvisi M, Bassi E, Civardi G. Pulmonary involvement in inflammatory bowel disease. *Curr Drug Targets Inflamm Allergy* 2004; 3:437-439.
9. Camus P, Piard F, Ashcroft T, Gal AA, Colby TV. The lung in inflammatory bowel disease. *Medicine* 1993; 72:151-183.
10. Bernstein CN, Wajda A, Blanchard JF. The clustering of other chronic inflammatory diseases in inflammatory bowel disease: a population-based study. *Gastroenterology* 2005; 29:827-836.
11. Douglas JG, McDonald CF, Leslie MJ, Gillon J, Crompton GK, McHardy GJ. Respiratory impairment in inflammatory bowel disease: does it vary with disease activity? *Respir Med* 1989; 83:389-394.
12. Songur N, Songur Y, Tuzun M, Doğan I, Tüzün D, Ensari A, Hekimoglu B. Pulmonary function tests and high-resolution CT in the detection of pulmonary involvement in inflammatory bowel disease. *J Clin Gastroenterol* 2003; 37:292-298.
13. Ceyhan BB, Karakurt S, Cevik H, Sungur M. Bronchial hyper-reactivity and allergic status in inflammatory bowel disease. *Respiration* 2003; 70:60-66.
14. Yilmaz A, Yilmaz Demirci N, Hoşgün D, Uner E, Erdoğan Y, Gökçek A, Çağlar A. Pulmonary involvement in inflammatory bowel disease. *World J Gastroenterol* 2010; 16:4952-4957.
15. Jose FA, Garnett EA, Vittinghoff E, Ferry GD, Winter HS, Baldassano RN, Kirschner BS, Cohen SA, Gold BD, Abramson O, Heyman MB. Development of extraintestinal manifestations in pediatric patients with inflammatory bowel disease. *Inflamm Bowel Dis* 2009; 15:63-68.
16. Krishnan S, Banquet A, Newman L, Katta U, Patil A, Dozor AJ. Lung lesions in children with Crohn's disease presenting as non resolving pneumonias and response to infliximab therapy. *Pediatrics* 2006; 117:1440-1443.
17. Carvalho RS, Wilson L, Cuffari C. Pulmonary manifestations in a pediatric patient with ulcerative colitis: a case report. *J Med Case Reports* 2008; 2:59.
18. Puntis JW, Tarlow MJ, Raafat F, Booth IW. Crohn's disease of the lung. *Arch Dis Child* 1990; 65:1270-1271.
19. Levenbrown Y, Tauber D, Hall OR, Baldrige AD. Granulomatous lung disease as the initial presentation of Crohn disease. *J Pediatr Gastroenterol Nutr* 2009; 48:487-490.
20. Bentur L, Lachter J, Koren I, Ben-Izhak O, Lavy A, Bentur Y, Rosenthal E. Severe pulmonary disease in association with Crohn's disease in a 13-year-old girl. *Pediatr Pulmonol* 2000; 29:151-154.
21. Akobeng AK, Miller V, Thomas AG. Unexplained chronic bronchial suppuration and inflammatory bowel disease. *J Pediatr Gastroenterol Nutr* 1999; 28:324-326.
22. Calder CJ, Lacy D, Raafat F, Weller PH, Booth IW. Crohn's disease with pulmonary involvement in a 3 year old boy. *Gut* 1993; 34:1636-1638.
23. Teague WG, Sutphen JL, Fechner RE. Desquamative interstitial pneumonitis complicating inflammatory bowel disease of childhood. *J Pediatr Gastroenterol Nutr* 1985; 4:663-667.
24. Mazer BD, Eigen H, Gelfand EW, Brugman SM. Remission of interstitial lung disease following therapy of associated ulcerative colitis. *Pediatr Pulmonol* 1993; 15:55-59.
25. Kayser K, Probst F, Gabius HJ, Müller KM. Are there characteristic alterations in lung tissue associated with Crohn's disease? *Pathol Res Pract* 1990; 186:485-490.
26. Al-Binali AM, Scott B, Al-Garni A, Montgomery M, Robertson M. Granulomatous pulmonary disease in a child: an unusual presentation of Crohn's disease. *Pediatr Pulmonol* 2003; 36:76-80.
27. Minic P, Perisic VN, Minic A. Metastatic Crohn's disease of the lung. *J Pediatr Gastroenterol Nutr* 1998; 27:338-341.
28. Le Roux P, Boulloche J, Briquet MT, Guyonnaud CD, Le Luyer B. Respiratory manifestation of Crohn's disease. apropos of a case in an adolescent. *Rev Mal Respir* 1995; 12:59-61.
29. Storch I, Sachar D, Katz S. Pulmonary manifestations of inflammatory bowel disease. *Inflamm Bowel Dis* 2003; 9:104-115.
30. Veloso F, Carvalho J, Magro F. Immune-related manifestations of inflammatory bowel disease: a prospective study of 792 patients. *J Clin Gastroenterol* 1996; 23:29-34.
31. Butland RJ, Cole P, Citron KM, Turner-Warwick M. Chronic bronchial suppuration and inflammatory bowel disease. *Q J Med* 1981; 50:63-75.
32. Eaton TE, Lambie N, Wells AU. Bronchiectasis following colectomy for Crohn's disease. *Thorax* 1998; 53:529-531.
33. Kelly MG, Frizelle FA, Thornley PT, Beckert L, Epton M, Lynch C. Inflammatory bowel disease and the lung: is there a link between surgery and bronchiectasis? *Int J Colorectal Dis* 2006; 21:754-757.
34. Fuschillo S. Bronchiectasis following total colectomy: inhaled steroids effect on lung function and bronchial inflammation. *Respir Med Extra* 2005; 1:134-136.
35. Mahadeva R, Walsh G, Flower CDR, Shneerson JM. Clinical and radiological characteristics of lung disease in inflammatory bowel disease. *Eur Respir J* 2000; 15:41-48.
36. Middleton SJ, Shorthouse M, Hunter JO. Increased nitric oxide synthesis in ulcerative colitis. *Lancet* 1993; 341:465-466.
37. Lundberg JO, Hellstrom PM, Lundberg JM, Alving K. Greatly increased luminal nitric oxide in ulcerative colitis. *Lancet* 1994; 344:1673-1674.
38. Reinders CA, Jonkers D, Janson EA, Stockbrügger RW, Stobering EE, Hellström PM, Lundberg JO. Rectal nitric oxide and fecal calprotectin in inflammatory bowel disease. *Scand J Gastroenterol* 2007; 42:1151-1157.
39. Koek GH, Vereleden GM, Evenepoel P, Rutgeerts P. Activity related increase of exhaled nitric oxide in Crohn's disease and ulcerative colitis: a manifestation of systemic involvement? *Respir Med* 2002; 96:530-535.
40. Ozyilmaz E, Yildirim B, Erbas G, Akten S, Oguzulgen IK, Tunc B, Tuncer C, Turktas H. Value of fractional exhaled nitric oxide (FE NO) for the diagnosis of pulmonary involvement due to inflammatory bowel disease. *Inflamm Bowel Dis* 2010; 16:670-676.
41. Fireman Z, Osipov A, Kivity S, Kopelman Y, Sternberg A, Lazarov E, Fireman E. The use of induced sputum in the assessment of pulmonary involvement in Crohn's disease. *Am J Gastroenterol* 2000; 95:730-734.
42. Swinburn CR, Jackson GJ, Cobden I, Ashcroft T, Morritt GN, Corris PA. Bronchiolitis obliterans organising pneumonia in a patient with ulcerative colitis. *Thorax* 1988; 43:735-736.
43. McCulloch AJ, McEvoy A, Jackson JD, Jarvis EH. Severe steroid responsive pneumonitis associated with pyoderma gangrenosum and ulcerative colitis. *Thorax* 1985; 40:314-315.
44. 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.
45. Hardarson S, Labrecque DR, Mitros FA, Neil GA, Goeken JA. Antineutrophil cytoplasmic antibody in inflammatory bowel

- and hepatobiliary diseases. High prevalence in ulcerative colitis, primary sclerosing cholangitis, and autoimmune hepatitis. *Am J Clin Pathol* 1993; 99:277–281.
46. Golpe R, Mateos A, Pérez-Valcárcel J, Lapeña JA, García-Figueiras R, Blanco J. Multiple pulmonary nodules in a patient with Crohn's disease. *Respiration* 2003; 70:306–309.
  47. Gabazza E, Taguchi O, Yamakami T, Machishi M, Ibata H, Fukukita S, Tsutsui K, Imoto I, Suzuki S, Kitagawa T. Bronchopulmonary disease in ulcerative colitis. *Intern Med* 1992; 31:1155–1159.
  48. Gibb W, Dhillon D, Zilkha K, Cole PJ. Bronchiectasis with ulcerative colitis and myelopathy. *Thorax* 1987; 42:155–156.
  49. Spira A, Grossman R, Balter M. Large airway disease associated with inflammatory bowel disease. *Chest* 1998; 113:1723–1726.
  50. Vandenplas O, Casel S, Delos M, Trigaux JP, Melange M, Marchand E. Granulomatous bronchiolitis associated with Crohn's disease. *Am J Respir Crit Care Med* 1998; 158:1676–1679.
  51. Veloso FT, Rodrigues H, Aguiar MM. Bronchiolitis obliterans in ulcerative colitis. *J Clin Gastroenterol* 1994; 19:339–341.
  52. Rickli H, Fretz C, Hoffman M, Walser A, Knoblauch A. Severe inflammatory upper airway stenosis in ulcerative colitis. *Eur Respir J* 1994; 7:1899–1902.
  53. 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.
  54. Patwardhan R, Heilpern J, Brewster A, Darrah JJ. Pleuropericarditis: an extraintestinal complication of inflammatory bowel disease. *Arch Intern Med* 1983; 143:94–96.
  55. Orii S, Chilba T, Nakadate I, Fujiwara T, Ito N, Ishii M, Oana S, Chida T, Kudara N, Terui T, Yamaguchi T, Suzuki K. Pleuropericarditis and disseminated intravascular coagulation in ulcerative colitis. *J Clin Gastroenterol* 2001; 32:251–254.
  56. Stajer D, Gorjup V. Myopericarditis, pleuritis and deep venous thrombosis in ulcerative colitis masquerading as pulmonary embolism. *Intensive Care Med* 1996; 22:1134–1135.
  57. Bernstein CN, Blanchard JF, Houston DS, Wajda A. The incidence of deep venous thrombosis and pulmonary embolism among patients with inflammatory bowel disease: a population-based cohort study. *Thromb Haemostasis* 2001; 85:430–434.
  58. Kappelman MD, Horvath-Puho E, Sandler RS, Rubin DT, Ullman TA, Pedersen L, Baron JA, Sorensen HT. Thromboembolic risk among Danish children and adults with inflammatory bowel diseases: a population-based nationwide study. *Gut* 2011; 60:937–943.
  59. Elzouki AN, Eriksson S, Lofberg R, Nässberger L, Wieslander J, Lindgren S. 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.
  60. Yang P, Tremaine W, Meyer RL, Prakash UB. Alpha-1 antitrypsin deficiency and inflammatory bowel diseases. *Mayo Clin Proc* 2000; 75:450–455.
  61. Lewis M, Kallenbach J, Zaltzman M, Levy H, Lurie D, Baynes R, King P, Meyers A. Severe deficiency of alpha 1-antitrypsin associated with cutaneous vasculitis, rapidly progressive glomerulonephritis and colitis. *Am J Med* 1985; 79:489–494.
  62. Karmy-Jones R, Chagpar A, Vallieres E, Hamilton S. Colobronchial fistula due to Crohn's disease. *Ann Thorac Surg* 1995; 60:466–468.
  63. Mera A, Sugimoto M, Fuduka K, Tanaka F, Imamura F, Matsuda M, Ando M, Shima K. Crohn's disease associated with colobronchial fistula. *Intern Med* 1996; 35:957–960.
  64. Munck A, Murciano D, Pariente R, Cezard JP, Navarro J. Latent pulmonary function abnormalities in children with Crohn's disease. *Eur Respir J* 1995; 8:377–380.
  65. Tzanakis N, Bouros D, Samiou M, Panagou P, Mouzas J, Manousos O, Siafakas N. Lung function in patients with inflammatory bowel disease. *Respir Med* 1998; 92:516–522.
  66. Herrlinger KR, Noftz MK, Dalhoff K, Ludwig D, Stange EF, Fellermann K. Alterations in pulmonary function in inflammatory bowel disease are frequent and persist during remission. *Am J Gastroenterol* 2002; 97:377–381.
  67. Mohamed-Hussein AA, Mohamed NA, Ibrahim ME. Changes in pulmonary function in patients with ulcerative colitis. *Respir Med* 2007; 101:977–982.
  68. Ateş F, Karıncaoğlu M, Hacıevliyagıl SS, Yalniz M, Seçkin Y. Alterations in the pulmonary function tests of inflammatory bowel diseases. *Turk J Gastroenterol* 2011; 22:293–299.
  69. Pasquis P, Colin R, Denis P, Baptiste P, Galmiche JP, Hecketsweiler P. Transient pulmonary impairment during attacks of Crohn's disease. *Respiration* 1981; 41:56–59.
  70. Mansi A, Cucchiara S, Greco L, Sarnelli P, Pisanti C, Franco MT, Santamaria F. Bronchial hyperresponsiveness in children and adolescents with Crohn's disease. *Am J Respir Crit Care Med* 2000; 161:1051–1054.
  71. Louis E, Louis R, Drion V, Bonnet V, Lamproye A, Radermecker M, Belaiche J. Increased frequency of bronchial hyperresponsiveness in patients with inflammatory bowel disease. *Allergy* 1995; 50:729–733.
  72. Marvisi M, Borrello PD, Brianti M, Fornarsari G, Marani G, Guariglia A. Changes in the carbon monoxide diffusing capacity of the lung in ulcerative colitis. *Eur Respir J* 2000; 16:965–968.
  73. Heatley RV, Thomas P, Prokipchuk EJ, Gaudie J, Sieniewicz DJ, Bienenstock J. Pulmonary function abnormalities in patients with inflammatory bowel disease. *Q J Med* 1982; 51:241–250.
  74. Bonniere P, Wallaert B, Cortot A, Marchandise X, Riou Y, Tonnel AB, Colombel JF, Voisin C, Paris JC. Latent pulmonary involvement in Crohn's disease: biological, functional, bronchoalveolar lavage and scintigraphic studies. *Gut* 1986; 27:919–925.
  75. Eade OE, Smith CL, Alexander JR, Whorwell PJ. Pulmonary function in patients with inflammatory bowel disease. *Am J Gastroenterol* 1980; 73:154–156.
  76. Wallaert B, Aerts C, Bonniere P, Cortot A, Tonnel AB, Paris JC, Voisin C. Superoxide anion generation by alveolar macrophages in Crohn's disease. *N Engl J Med* 1985; 312:444–445.
  77. Higgenbottom TW, Cochrane GM, Clark TJH, Turner D, Millis R, Seymour W. Bronchial disease in ulcerative colitis. *Thorax* 1980; 35:581–585.
  78. Tunc B, Filik L, Bilgic F, Arda K, Ulker A. Pulmonary function tests, high resolution computed tomography findings and inflammatory bowel disease. *Acta Gastroenterol Belg* 2006; 69:255–260.
  79. Smart HL, Mayberry JF. Atopy, food and ulcerative colitis. *Hepato-gastroenterology* 1986; 33:47–48.
  80. Raj AA, Birring SS, Green R, Grant A, de Caestecker J, Pavord ID. Prevalence of inflammatory bowel disease in patients with airways disease. *Respir Med* 2008; 102:780–785.
  81. Pugh SM, Rhodes J, Mayberry JF, Roberts DL, Heatley RV, Newcombe RG. Atopic disease in ulcerative colitis and Crohn's disease. *Clin Allergy* 1979; 9:221–223.
  82. Roberts DL, Rhodes J, Heatley RV, Newcombe RG. Atopic features in ulcerative colitis. *Lancet* 1978; 1:1262.
  83. Mee AS, Brown D, Jewell DP. Atopy in inflammatory bowel disease. *Scand J Gastroenterol* 1979; 14:743–746.
  84. Jewell DP, Truelove SC. Reaginic hypersensitivity in ulcerative colitis. *Gut* 1972; 13:903–906.
  85. Fireman E, Masarwy F, Groisman G, Shtark M, Kopelman Y, Kivity S, Fireman Z. Induced sputum eosinophilia in ulcerative colitis patients: the lung as a mirror image of intestine? *Respir Med* 2009; 103:1025–1032.
  86. Collins JR. Adverse reactions to salicylazosulfapyridine (azulfidine) in the treatment of ulcerative colitis. *South Med J* 1968; 61:354–358.
  87. Parry SD, Barbatzas C, Peel ET, Barton JR. Sulphasalazine and lung toxicity. *Eur Respir J* 2002; 19:756–764.
  88. Imokawa S, Colby T, Leslie K, Helmers RA. Methotrexate pneumonitis: review of the literature and histopathologic findings in nine patients. *Eur Respir J* 2000; 15:373–381.

89. Ananthakrishnan AN, Attila T, Otterson MF, Lipchik RJ, Massey BT, Komorowski RA, Binion DG. Severe pulmonary toxicity after azathioprine/6-mercaptopurine initiation for the treatment of inflammatory bowel disease. *J Clin Gastroenterol* 2007; 41:682–688.
90. Keane J, Gershon S, Wise RP, Mirabile-Levens E, Kasznica J, Schwiertman WD, Siegel JN, Braun MM. Tuberculosis associated with infliximab, a tumor necrosis factor alpha-neutralizing agent. *N Engl J Med* 2001; 345:1098–1104.
91. Treiber G. Mycophenolate mofetil for therapy-resistant interstitial lung disease associated with ulcerative colitis. *Am J Gastroenterol* 2000; 95:3674–3675.
92. Alrashid AI, Brown RD, Mihalov ML, Sekosan M, Pastika BJ, Venu RP. Crohn's disease involving the lung: resolution with infliximab. *Dig Dis Sci* 2001; 46:1736–1739.
93. Rosen MJ. Chronic cough due to bronchiectasis: ACCP evidence-based clinical practice guidelines. *Chest* 2006; 129:122S–131S.

Address correspondence to:

*Yakov Sivan, M.D.*

*Department of Pediatric Pulmonology*

*Critical Care and Sleep Medicine*

*Dana Children's Hospital*

*Tel Aviv Sourasky Medical Center*

*6 Weitzman St.*

*Tel Aviv 64239*

*Israel*

*E-mail: sivan@post.tau.ac.il*

Received for publication March 9, 2011; accepted after revision October 3, 2011.

**This article has been cited by:**

1. Philippe Camus . 2011. Chest Involvement in Inflammatory Bowel Disease. *Pediatric Allergy, Immunology, and Pulmonology* 24:4, 181-185. [[Citation](#)] [[Full Text](#)] [[PDF](#)] [[PDF Plus](#)]