

2 year old boy with failure to thrive

ATS 2017

Presenter:

Apeksha Sathyaprasad, MD
Pediatric Pulmonary Fellow

**St. Louis Children's Hospital/ Washington University in
St. Louis**

Discussant:

Folasade O. Ogunlesi, MD

Assistant Professor of Pediatrics

**Children's National Medical Center/ The George
Washington University School of Medicine & Health
Sciences**



History of Present Illness

2 year old African-American male admitted for *septic shock, multiorgan dysfunction syndrome* due to *central line associated candidemia*

Initially presented to pediatrician's office in respiratory distress and ultimately admitted to the PICU

- Respiratory failure- intubated and on mechanical ventilatory support
- Septic shock- vasopressors
- Renal failure- continuous veno-venous hemofiltration

Pulmonology consulted on hospital day #10 because of prolonged mechanical ventilatory support

Past Medical History

Born full-term, birth weight 3.318 Kg. Pregnancy, delivery, newborn period was unremarkable. Did not require oxygen support, no history of delayed passage of meconium. No history of chronic persistent rhinitis or cough

1 year of age- chronic diarrhea and poor weight gain

- Endoscopy, contrast imaging, hepatic enzymes, anti-tTG: unremarkable
- Dietary modifications (higher calorie elemental formula)
- G-tube with Nissen fundoplication
- Chronic intravenous hyperalimentation

Central line-associated blood stream infection

- *S. viridans*, *Klebsiella*, *E.coli*, *Enterococcus*, *S. aureus*

History of eczema, intermittent cough and wheezing with viral illnesses which reportedly responded to treatment with inhaled albuterol

Family and social history

Family History: Grandmother has recurrent sinusitis. No history of asthma, cystic fibrosis, recurrent infections, infertility, gastrointestinal diseases

Social history: Lives with mother and grandmother. Does not attend daycare. No second-hand tobacco exposure. No avian or agricultural exposures. No pets. No history of travel outside the United States

Physical Examination

Vital signs:

T: 98.8 degrees F, **HR:** 113 beats/min, **BP:** 108/68 mm Hg, **RR:** 40 breaths/min

Ventilator support:

SIMV PRVC, FiO₂ 0.40, rate 34/min, Vt 95 mL, PEEP 8 cm H₂O, PS 20 cm H₂O

Oxyhemoglobin saturation: 100%

Growth percentiles:

- Height: 80cm (1%ile)
- Weight: 8.9 Kg (1%ile)
- BMI: <1%ile; BMI-Z score: -2.59
- HC: 47.3 cm (18%ile)

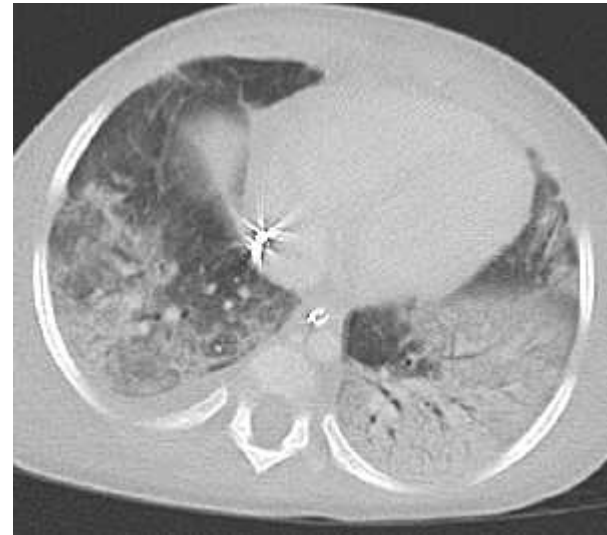
Physical Exam

- **HEENT:** Normal
- **Neurologic:** Sedated; Pupils equal and reactive
- **Pulmonary:** *bilateral good air entry, diffuse crackles most prominent over the RUL, no wheezing*
- **Cardiovascular:** Regular rate and rhythm, no murmurs
- **Abdomen:** Soft, non-distended, non-tender, no masses palpated, normal bowel sounds
- **Extremities:** No clubbing, cyanosis or edema
- **Skin:** Eczematous lesions over extensor surface of the elbows and knees

Chest imaging studies



Chest imaging studies



Laboratory evaluation

- **CBC:** WBC **23,000/mm³** (neutrophils 71%, band neutrophils **5%**, metamyelocytes **1%**, lymphocytes 18%, Hgb **9.6 g/dL**, Hct 36%, platelet **30,000/mm³**;
- ABG at time of consultation: **7.4/60/134**
- Blood culture (fungal): ***Candida tropicalis***
- **Bronchoscopy with bronchoalveolar lavage** - thick purulent secretions throughout airways, primarily from the right upper lobe
- ENT evaluation of upper airway: **normal**
- Ciliary ultrastructure: **normal**
- Sweat chloride concentration: **9 mmol/L**
- Immunological evaluation: **nondiagnostic**

Summary

- 2 year old African-American boy
- Growth failure, malabsorption of unknown etiology, TPN dependent
- Airway hyperreactivity, eczema
- Recurrent central venous catheter infections
- Candidemia and septic shock with multi-organ dysfunction syndrome
- Right upper lobe bronchiectasis, diffuse interstitial and alveolar infiltrates

Audience response question

What is the likely cause of this child's bronchiectasis and failure to thrive?

1. Cystic fibrosis
2. Primary ciliary dyskinesia
3. Severe combined immunodeficiency
4. Severe gastroesophageal reflux with pulmonary aspiration
5. I don't know, teach me!

Bronchiectasis

Abnormal, irreversible dilation of the airways
Viscous cycle leading to airway damage

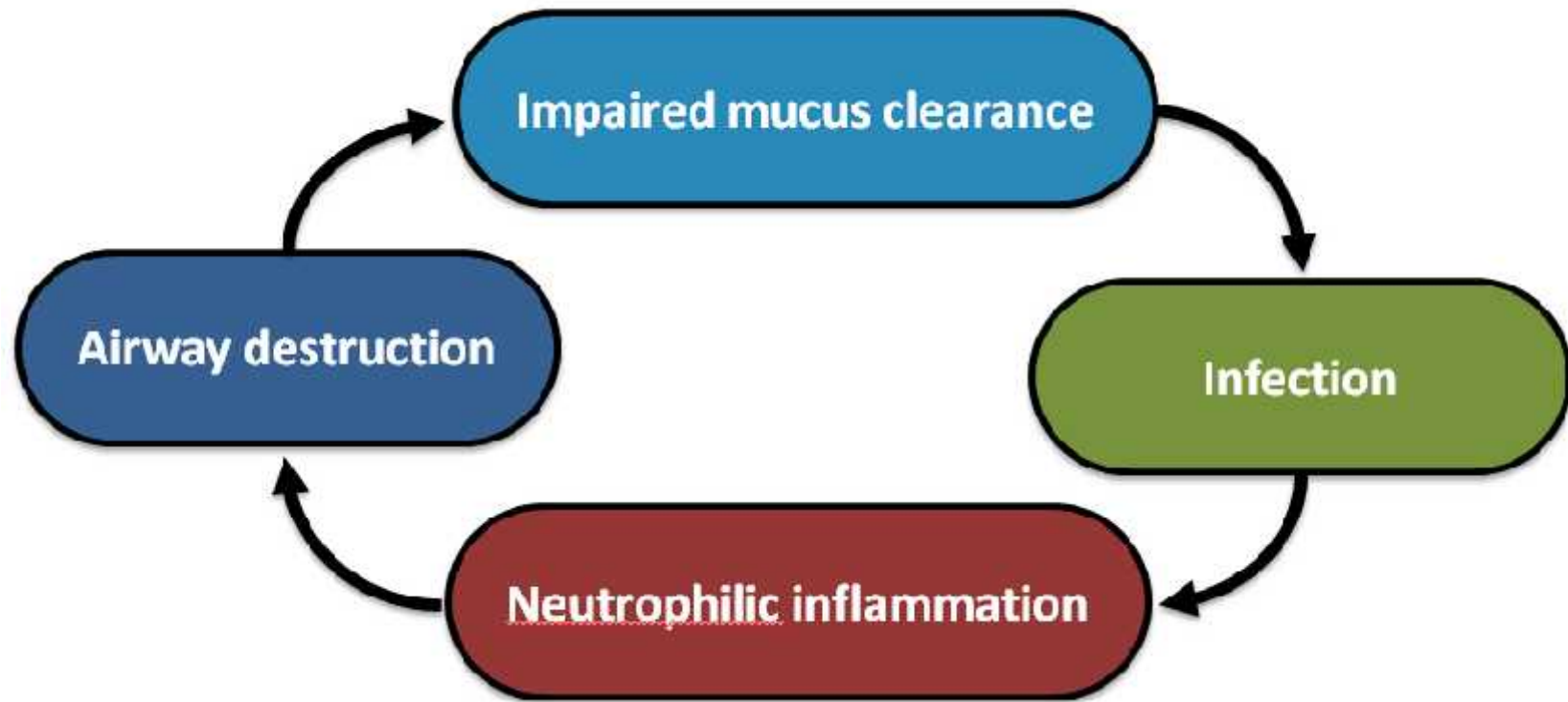


Figure: Thomas Ferkol MD.

Etiologies of non-Cystic Fibrosis Bronchiectasis in childhood (N =989)

Underlying etiology	Number	% of total
Primary immunodeficiency B Cell disorders(73.5%) T cell disorders (7.5%) Common variable immunodeficiency (CVID) (10%)	160	18%
Secondary immunodeficiency Post Chemotherapy HIV/AIDS		62% 18%
Aspiration Recurrent aspiration (seizures) TEF with recurrent pneumonia/ Cystic Lung ds Retained foreign body	95 14 18	10% 15% 52%; 19% 20%
Infectious Pneumonia(Viral/Bacterial)(61%) Measles (14%) Tuberculosis (11%) Pertussis Post Adenovirus; ABPA	173	19%
Primary ciliary dyskinesia	91	10%
Idiopathic	308	34%

Brower, et al. *BMC Pediatr.* 2014; 14:299

Primary Immunodeficiencies associated with non-CF Bronchiectasis

	Total number	% of total
B cell disorders	97	74%
• IgG deficiency	63	48%
• IgG subclass deficiency	24	18%
• IgA deficiency	9	7%
• B cell deficiency NOS	1	1%
T cell disorders	9	7%
• Hyper IgE syndrome	3	2%
• Hyper IgM syndrome	2	2%
• T cell deficiency	3	2%
• Chronic Mucocutaneous Candidiasis	1	1%
Combined Immunodeficiency	13	10%
• Severe combined immunodeficiency	9	7%
• Ataxia telangiectasia	2	2%
• Wiskott-Aldrich syndrome	2	2%
Chronic granulomatous disease	7	5%
Barre lymphocyte syndrome MHC class II deficiency	2	2%
Mannose-binding protein def	1	1%
Others	2	2%

Brower, et al. *BMC Pediatr.* 2014; 14:299

Differential for bronchiectasis and poor weight gain

- Cystic fibrosis
- Cellular immunodeficiency with recurrent pneumonia
- Primary ciliary dyskinesia
- Gastroesophageal reflux with aspiration pneumonia
- Other: Inflammatory bowel disease

Clinical course

- Continued treatment with intravenous amphotericin B
- **Non-CF bronchiectasis:** airway clearance with high-frequency chest wall oscillation, hypertonic saline
- **Airway hyperreactivity:** Daily inhaled corticosteroids and albuterol as needed
- Patient was extubated and eventually placed on oxygen flow via nasal cannula at 1 L/min

Audience response question

Which of the following is not recommended for the routine management of non-CF bronchiectasis?

1. Bronchodilators
2. Chest physiotherapy
3. Macrolide antibiotics
4. Recombinant human Deoxyribonuclease

Audience response question

Which of the following is not recommended for the routine management of non-CF bronchiectasis?

1. Bronchodilators
2. Chest physiotherapy
3. Macrolide antibiotics
4. Recombinant human Deoxyribonuclease

Management of non-CF bronchiectasis

- **Airway clearance**
- **Antibiotics** for acute exacerbations, based on respiratory culture results. Long-term antibiotics (inhaled or oral) should not be prescribed routinely
- **Immunizations** including annual influenza vaccine

- **Azithromycin:** decreased frequency of exacerbations. Rule out chronic Nontuberculous Mycobacterium infection prior to initiation of therapy
- **Mucoactive agents:** Hypertonic Saline and Mannitol may improve clearance of mucus
- **Bronchodilator** therapy may be useful in patients who have evidence of airway hyperreactivity
- **Inhaled and systemic corticosteroids** should not be routinely prescribed unless there is an established diagnosis of coexisting asthma

J. McShane, et al. *Am J Respir Crit Care Med.* 2013; 188(6):647-56

Management of non-CF bronchiectasis

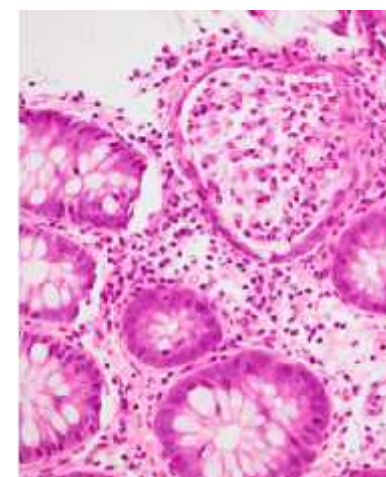
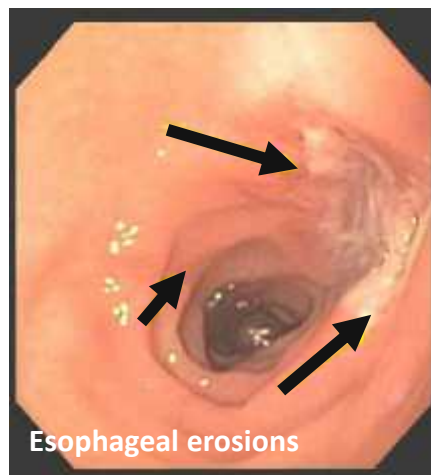
- 349 adults with idiopathic bronchiectasis, stable disease received aerosolized dornase alfa or placebo twice daily for 24 weeks
- Pulmonary exacerbations were more frequent and FEV1 decline was greater in patients who received the inhaled mucolytic agent compared with placebo

	Placebo	Treatment	Relative risk
Protocol defined exacerbations	0.56	0.66	1.17
Non-protocol defined exacerbations	0.14	0.29	2.01
Total exacerbations	0.71	0.95	1.35

O'Donnell AE, *et al. Chest* 1998; 113:1329-34

Follow-up evaluation

- Re-presented with rectal bleeding and underwent endoscopy



- **Endoscopic biopsy** of large intestine, ascending colon - focal active colitis with cryptitis, crypt microabscesses and surface erosion
- Consistent with **Crohn disease**

Management

- Treated with prednisone, 2mg/kg/day and gradually decreased over a 3 month period
- Azathioprine, 2mg/kg once daily
- Within 3 months, the child no longer required supplemental oxygen

Inflammatory Bowel Disease (IBD)

Epidemiology

- Systemic disorder; unknown etiology; primarily involving the GI tract
- 25% have extra-intestinal manifestations: pulmonary involvement, arthritis, uveitis, erythema nodosum, pyoderma gangrenosum, primary sclerosing cholangitis
- **Incidence:** peaks in 2nd decade between ages 15 and 30 years
- All IBD patients: diagnosed in the pediatric age group:
CD: 25 - 30% **UC:20%**
- Crohn disease (CD): patchy transmural inflammation of GI tract, from mouth to the perianal area

Inflammatory bowel disease and the lungs

- No precise data on the **prevalence** of IBD-associated lung involvement in children
 - 7 patients less than 2 years with Crohn disease;
 - 1 patient - 1 month old *had pulmonary infiltrates from age of 7 months.*
 - **Bronchoalveolar lavage** – *no infectious etiology*
 - **Open lung biopsy** @ 4.5 years old- *multiple granulomas with chronic inflammation and minimal fibrosis*

George Marx, *The Journal of Pediatrics* 2002; Vol. 140, (4)470–473;

Inflammatory bowel disease and the lungs - pathogenesis

Mechanism:

- Common embryological origin of the **GI tract & lung**
- **Similar immune systems in mucosa**; presence of circulating immune complexes and auto-antibodies
- Adverse pulmonary effects of some drugs
- Respiratory involvement may precede bowel disease presentation by months or years
- Colonic surgery may promote onset of respiratory symptoms

- Lu, De-Gan et al. *World J Gastroenterol* 2014; 20.1: 133–141.
- Camus P et al. *Eur Respir J* 2000; 15:5–10,
- Eaton TE et al. *Thorax* 1998;53:529-531.

Inflammatory bowel disease and the lungs - pathogenesis

- AIRWAY INFLAMMATION – most prevalent pattern of respiratory involvement
- AIRWAY DISEASE – Large and small airways
- LUNG PARENCHYMA
- PLEURAL DISEASE

Majewski *et al. Arch Med Sci.* 2015 10; 11(6): 1179–1188
Schleiermacher, *et al. J Crohns Colitis* 2007; 2007, 61–69

Airway involvement

- **Bronchiectasis:** single most common pulmonary manifestation of IBD; Can present at any stage
 - 66% of patients with IBD
- **Airway nodules**
- **Upper airway obstruction and tracheobronchitis:** mucosal inflammation, ulceration, fibrosis and narrowing/ subglottic stenosis

Clinical symptoms: cough, copious sputum production, stridor, SOB

Black *et al.* *Chest*, 2007; 131(2):524-32



Left mainstem bronchus stenosis in a patient with CD

Parenchymal disease

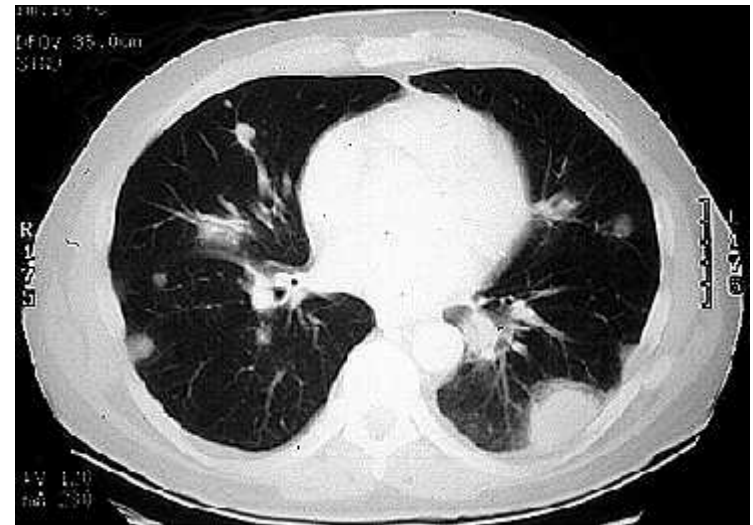
Clinical symptoms: fever, cough, dyspnea, pleuritic chest pain

- **Cryptogenic organizing pneumonia (COP)**- may accompany pulmonary infection or manifestation of drug toxicity
- **Interstitial lung disease:** Unspecified Interstitial lung disease, Eosinophilic pneumonia, Nonspecific interstitial pneumonia, Desquamative interstitial pneumonia, Usual interstitial pneumonia
- Pulmonary Interstitial Emphysema syndrome
- Fibrosing alveolitis

Majewski *et al. Arch Med Sci.* 2015 10; 11(6): 1179–1188
Schleiermacher, *et al. J Crohns Colitis* 2007; 2007, 61–69

Parenchymal disease- pulmonary nodules

- Infrequently reported:
 - necrobiotic nodules (25%)
 - non-caseating granuloma (12.5%)
- May frequently cavitate
- **Histopathology:** Sterile aggregates of neutrophils with necrosis
- **Differentials:** septic pulmonary emboli or granulomatosis with polyangiitis



©2016 UpToDate®

Majewski *et al. Arch Med Sci.* 2015 10; 11(6): 1179–1188

Xiao-Qing Ji *et al. World J Gastroenterol.* 2014; 20(37): 13501–13511.

Enteric-pulmonary fistulae

- Occurs infrequently
- Recurrent pneumonia with feculent sputum in patients with CD should raise suspicion of **colobronchial fistula**
- **Colopleural fistula** and **fecopneumothorax** are rare, but life-threatening complications of CD
- Abdominal and thoracic CT scans or magnetic resonance imaging (MRI)
- Treatment: mandatory surgery

Storch I *et al. Inflamm Bowel Dis.* 2003; 9(2):104-15

Xiao-Qing Ji *et al. World J Gastroenterol.* 2014; 20(37): 13501–13511

Pleural disease:

- Serositis causing pleural and pericardial effusion
- Fluid is exudative containing neutrophils; may be hemorrhagic
- **Drug induced – Biologic agents, 5-ASA, Methotrexate**

- Pneumothorax
- Pleural thickening
- Pleuritis

Rosenbaum AJ et al. J Clin Gastroenterol. 1983 J Clin Gastroenterol. 1983

Airway hyperreactivity

- **Methacholine challenge:**
 - Bronchoprovocation challenges are usually negative
 - Increased bronchial hyperresponsiveness in 14 children with CD compared to control subjects, although the provocative dose causing a 20% fall in FEV1 in CD patients was greater than in the 10 asthmatics also tested in the study
- Inflammation of the airways by inflammatory cells and their products

Bartholo RM *et al. Braz J Med Biol Res.* 2005;38(2):197-203
Black, *et al. Chest,* 2007; 131(2):524-32

Pulmonary function abnormalities

- **Spirometry** - reduced or normal FVC, FEV1, low FEV1/FVC; no significant reversibility with bronchodilator
- **Fractional eNO:** significantly higher in CD patients and correlated positively with CD activity
- **Diffusion capacity for carbon monoxide :**
 - Decreased in asymptomatic IBD patients
 - Significantly lower in patients with active GI disease than those in remission

Welsh L *et al.* *Am J Respir Crit Care Med* 2012; 15;186(10):1060-1

Bronchoscopy

Bronchoscopy - chronic inflammation in the lungs of IBD patients

Bronchoalveolar lavage fluid (BAL)

- To identify infectious etiology
- Asymptomatic patients with CD
 - Persistently elevated alveolar lymphocytosis
 - An elevated CD4:CD8 ratio in the BAL, a characteristic finding in sarcoidosis, has also been documented in patients with CD
 - There is no correlation with drug treatment or CD activity

Black, *et al. Chest*, 2007; 131(2):524-32

Bewig B, *et al. Respiration*. 1999;66(5):467-9

TREATMENT

- **Corticosteroids** have demonstrated a high efficiency in inducing clinical remission
- **Immunomodulatory agents**
Azathioprine, Methotrexate, 6 mercaptopurine
- **Biologics** (anti-TNF drugs) – significant advance in CD
 - Infliximab, Adalimumab, Certolizumab
- Can maintain remission and improve some of the pulmonary manifestations of IBD

Drugs used for IBD

Several of these agents can cause direct pulmonary toxicity:

- Organizing pneumonia (**Azathioprine, 6-Mercaptopurine**)
- Nonspecific interstitial pneumonitis (**Azathioprine, 6-Mercaptopurine, Methotrexate, Sulfasalazine, Mesalamine**)
- Eosinophilic pneumonitis (**Sulfasalazine, Mesalamine, Methotrexate**)
- Pulmonary fibrosis (**Methotrexate**)
- Lupus-like syndrome with serositis (**Biologic agents, 5-ASA, Mesalamine**)
- Drug-induced hypersensitivity (**Methotrexate**)
- Opportunistic infections (**Biologic agents**)

Discontinuation the offending agent usually results in improvement

De-Gan Lu, *et al.* *World J Gastroenterol* 2014;7;20(1): 133-141

Take home points

- Maintain a high index of suspicion for lung disease in patients with inflammatory bowel disease
- Lung disease can involve airways or parenchyma and could be due to:
 - Underlying IBD
 - Opportunistic infections
 - Pulmonary toxicity of medications used for treatment of IBD
- Diagnostics: Chest imaging, Spirometry, DLCO and FeNO
- Bronchoscopy, Bronchoalveolar lavage, +/- Biopsy

Thank you!
Questions?



Children's National Medical Center

St. Louis Children's Hospital