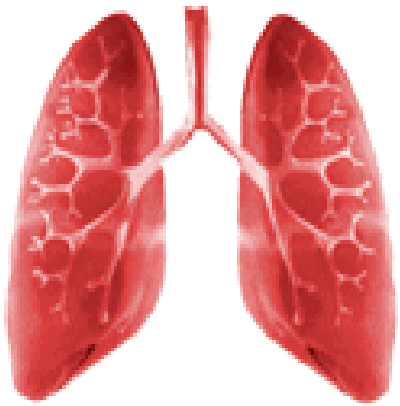
Cryptogenic Organizing Pneumonia

Presented by: Eleni Martinez, Pharm.D.

PGY1 Pharmacy Resident

April 2nd, 2015



Objectives

- Define cryptogenic organizing pneumonia (COP)
- Describe the pathogenesis and epidemiology for COP
- Explain symptoms and diagnostic tools for COP
- Discuss treatment and management strategies for COP
- Evaluate a treatment plan for a patient with COP based on a patient case

Background

- Bronchiolitis obliterans organizing pneumonia (BOOP) was first described by Gary Epler in 1985
- Characterized by
  - Sub-acute or chronic respiratory illness
  - Presence of granulation tissue in the bronchiolar lumen, alveolar ducts and some alveoli
- Number of known causes for BOOP
  - Idiopathic if the cause cannot be identified

BOOP: Bronchiolitis obliterans organizing pneumonia

King, TE Jr. Cryptogenic Organizing Pneumonia. UpToDate. 2014. Available at: http://www.uptodate.com/contents/cryptogenic-organizing-pneumonia?

Background

- Secondary causes for BOOP
  - Post-respiratory infection
  - Drug-related
  - Radiation therapy
  - Organ transplantation
  - Occupational/environmental
  - Miscellaneous causes
- Primary, idiopathic BOOP is now referred to as cryptogenic organizing pneumonia (COP)

BOOP: Bronchiolitis obliterans organizing pneumonia

Epler GR. Bronchiolitis obliterans organizing pneumonia, 25 years: a variety of causes, treatment options?. Expert Rev Respir Med. 2011;5(3):353-61.

Patient Case

- PG is a 54 year old female who had a complicated hospital stay from 2/15-3/10/15
- PMhx
  - Frequent pneumonia since childhood
- FMhx
  - (+) colon and bone cancer
- SChx
  - Quit smoking (smoked 1 pack per week for 10 years)
  - (-) alcohol, (-) illicit drug use
  - Works as an LPN for a local doctor's office
- Home meds
  - Zolpidem CR 12.5mg orally at bedtime

Patient Case

- CC: Shortness of breath
- PE: Pleasant, well-developed, well-nourished, Caucasian female in no acute distress
- BP: 141/93, HR: 144, Temp: 97.9°F, O^2 sat: 92
- Ht: 5'2", Wt: 52.6kg
- Chest X-ray: No acute cardiopulmonary process identified

Labs (2/15)	Values
Na	148
K	4.1
Cl	103
CO_2	31
SCr	0.8
BUN	18
Glucose	98
Troponin	<0.02
WBC	18.6
Bands	2

Patient Case

- Seen at Hamilton County Employee Clinic
  - Received corticosteroids and cough medicine
  - Returned in 5 days and received Clarithromycin course
- Admitted to Memorial Hixson on 2/15-2/21/15 with a 2-week history of cough and dyspnea
  - Unresponsive to outpatient antibiotics and corticosteroids
  - Admitting diagnosis: COPD exacerbation/acute bronchitis
  - Sent home on nebulizer treatment with albuterol, prednisone taper, and course of levaquin

Introduction

- COP is a rare inflammatory lung disorder
- Interstitial lung disease that affects the:
  - Distal bronchioles
  - Respiratory bronchioles
  - Alveolar ducts
  - Alveolar walls
- Organizing pneumonia refers to organized areas of inflammatory tissue that fill the bronchioles and alveoli
- Term “cryptogenic” means the cause is unknown

COP: Cryptogenic Organizing Pneumonia

Bronchiolitis Obliterans Organizing Pneumonia. 2013. Available at: http://www.rarediseases.org. Accessed April 2, 2015.

Symptoms

- Symptoms develop slowly over a few weeks or months
- Most common features include:
  - Persistent nonproductive cough
  - Dyspnea
  - Fever
  - Malaise
  - Weight loss of greater than 10 pounds

King TE Jr. Organizing pneumonia. In: Interstitial lung disease, 5, Schwarz MI, King TE Jr. (Eds), People's Medical Publishing House, Shelton, CT 2011. p.981

Pathogenesis

- Inflammation of lungs caused by series of events

Leakage of plasma proteins

↓

Recruitment of fibroblasts

↓

Fibrin formation within the alveolar lumen

↓

Alveolar epithelial injury

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Epidemiology

- 1.1 to 7 cases per 100,000 hospital admissions annually
- Approximately 56 to 68 percent of cases have been deemed cryptogenic
- Most common in individuals ages 40 to 60
- 5-10 percent of chronic infiltrative lung disease in the U.S.
- Smoking ≠ precipitating factor

Bronchiolitis Obliterans Organizing Pneumonia. 2013. Available at: http://www.rarediseases.org. Accessed April 2, 2015.

Physical Exam

- Physical exam
  - Inspiratory crackles or rales
- In rare cases patients may present with:
  - Wheezing
  - Arthralgia
  - Night sweats
- Lack of clinical response to empiric antibiotics along with physical exam may raise questions of COP

COP: Cryptogenic Organizing Pneumonia

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Diagnostic Tools

- Chest x-ray
  - Bilateral, patchy or diffuse, consolidative or ground glass opacities in the presence of normal lung volumes
- CT scan
  - Triangular-shaped ground-glass opacities
- Pulmonary function testing
  - Decrease in vital capacity
- Bronchoalveolar lavage
  - May show high percentage of lymphocytes
- Transbronchoscopic or surgical lung biopsy
  - Rule out other differential diagnoses

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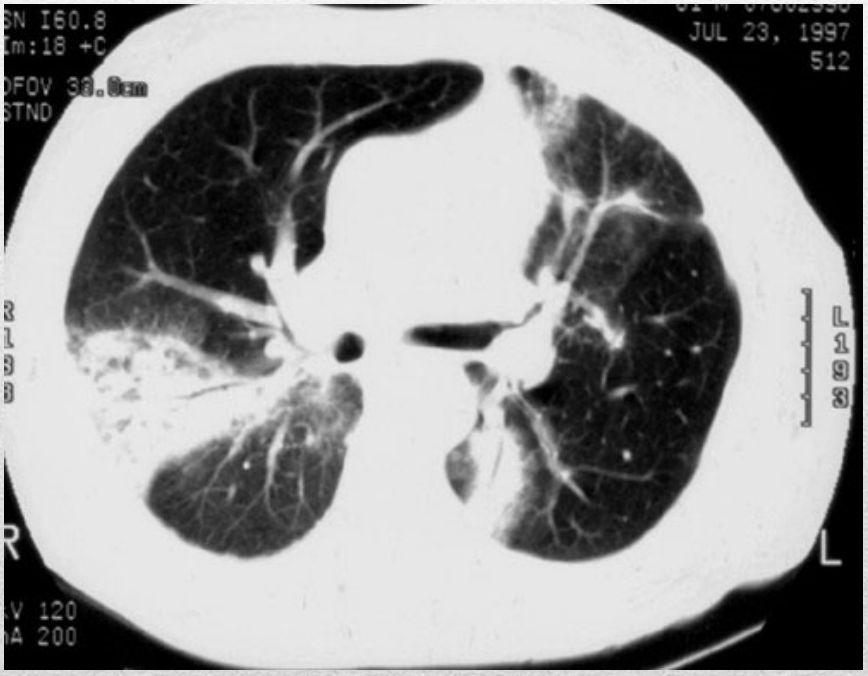
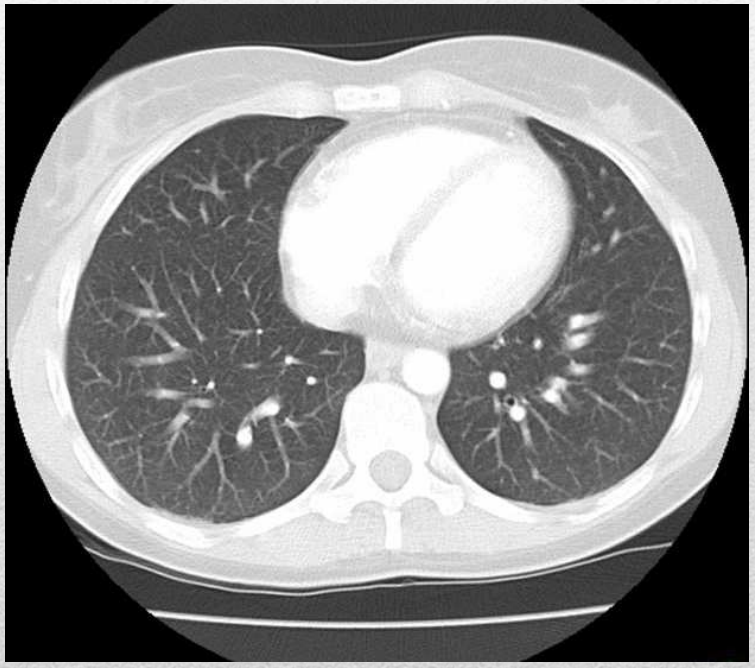
Diagnostic Tools

Abnormal Chest CT (COP)



Normal Chest CT



COP: Cryptogenic Organizing Pneumonia

Diagnostic Tools

- Laboratory testing
  - CBC with diff, BUN, SCr, LFT, UA, ESR, CRP
    - Leukocytosis observed in around 50 percent of patients
    - Positive CRP observed in 70-80 percent
- Additional tests
  - Blood cultures, sputum gram stain, sputum enzyme immunoassay (EIA) or polymerase chain reaction (PCR)
- Tests for connective tissue disorders
  - Antinuclear antibody, rheumatoid factor, creatine kinase, anti-topoisomerase, and anti-double-stranded DNA

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Treatment

- Treatment of COP has not been studied in randomized trials
- Therapy is initiated based on severity of disease

Mild	Mild to Moderate	Severe
Monitor	Monitor or Treat	Treat

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Treatment

- Corticosteroids are the current standard treatment
- Prednisone is the preferred agent
  - 0.75 to 1mg/kg/day for 1 to 3 months
  - 0.75 to 0.5mg/kg/day for 3 months
  - 10 to 20 mg/day or every other day for a total of 1 year
- Patients should be followed with a chest x-ray and pulmonary function test every 2-3 months
- Adverse effects
  - Infection, hyperglycemia, weight gain, osteoporosis, adrenal suppression

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Treatment

- Cytotoxic therapy can be added for patients who fail to improve with glucocorticoids
- Oral cyclophosphamide is commonly used
  - 1 to 2mg/kg/day up to a maximum of 150mg/day
  - Usually start at 50mg daily and increase over 2 to 4 weeks
  - Treatment is usually 6 months due to toxicity
  - Adverse effects
    - Bone marrow suppression, increased susceptibility to infection, and gonadal toxicity,

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Treatment

- Macrolides (3-month course)
  - Intolerant to steroid therapy or add-on agent
  - Azithromycin 250mg orally three times weekly
  - Clarithromycin 500mg orally twice daily
- Other immunosuppressive agents
  - Azathioprine 100-125mg orally daily
  - Mycophenolate mofetil 1,000mg orally twice daily
  - Cyclosporine A 75-100mg orally twice daily

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Considerations for Fulminant Disease

- IV glucocorticoids
  - Methylprednisolone 125 to 250 mg every 6 hours
  - Methylprednisolone 750 to 1000 mg daily for 3 to 5 days
- Patients can be transitioned to oral prednisone once they show signs of improvement
- IV cyclophosphamide is often added to patients
  - Require mechanical ventilation
  - Do not respond rapidly to intravenous glucocorticoids

Bradley B, Branley HM, Egan JJ, et al. Interstitial lung disease guideline: the British Thoracic Society . Thorax. 2008;63 Suppl 5:v1-58.

Prognosis

- Two-thirds of patients treated with glucocorticoids completely recover
  - Total clinical and physiologic improvement and normalization of the chest x-ray
- Most patients improve over several weeks to a few months
  - Symptomatic improvement may occur in 1 to 2 weeks

Lee JW, Lee KS, Lee HY, et al. Cryptogenic organizing pneumonia: serial high-resolution CT findings. AJR Am J Roentgenol. 2010;195(4):916-22.

Patient Case

- Readmitted on 2/22/15
  - Persistent cough, fever, chills, hypoxemia and leukocytosis
  - Admitting diagnosis: COPD exacerbation/HCAP
  - Chest CT and chest x-ray abnormal
  - Sputum cultures obtained
  - Bronchial lavage on 2/27 shows aspergillus
  - Transferred for open lung biopsy

Patient Case

- BP: 119/57, HR: 127, Temp: 98.6°F, O^2 sat: 94
- Lungs: Slight inspiratory crackles
- Chest CT: Diffuse areas of groundglass attenuation throughout both lungs
- Chest X-ray: Asymmetric interstitial infiltrates

Labs (2/22)	Values
Na	136
K	4.5
Cl	102
CO_2	29
Scr	0.6
BUN	14
Glucose	113
Troponin	<0.02
WBC	28.5
PCT	<0.05

Patient Case

- Transferred to Glenwood on 3/4/15
  - Treated with broad spectrum antibiotics
  - Lung biopsy showed acute interstitial lung process
  - Bronchial biopsy negative
- Imaging
  - Chest X-ray on 3/4/15
    - Mildly enlarging patchy infiltrates
  - Chest CT on 3/7/15
    - Diffuse hazy ground glass infiltrates throughout both lungs

Patient Case

- Pertinent Lab Trends

Date	Labs	Values
3/7	CRP	135
3/25	CRP	<2.9
2/26	ESR	21
3/7	ESR	39

- CRP and ESR are inflammatory markers
- Monitoring the progress of COP using these has been recommended but remains nonspecific and unreliable

CRP: C-Reactive Protein
ESR: Erythrocyte sedimentation rate

Patient Case

- Pathology Results 3/9
  - Multifocal organizing pneumonia with mild background interstitial fibrosis
- Treatment
  - Solu-Medrol IV 60mg every 6 hours for 3 days
  - Prednisone 40mg orally daily
  - Antibiotics were discontinued once prednisone was started

Patient Case

- Discharge on 3/10
  - Follow-up with PCP in 1 week
  - Follow-up with pulmonary in 4 weeks
- Pertinent Discharge Medications
  - Prednisone 40mg daily until pulmonary follow-up
  - Duonebs four times daily
- Pulmonary recommended discontinuation of antimicrobial therapy
  - All labs were within normal limits at discharge

Take Home Points

- COP is an idiopathic, inflammatory, non-infectious type of pneumonia
- Due to the similar clinical presentation, many patients are first misdiagnosed with CAP
- **Gold Standard: long-term/high dose glucocorticoid therapy**
- Pharmacists can play a vital role in making recommendations and counseling patients

References

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6. Lee JW, Lee KS, Lee HY, et al. Cryptogenic organizing pneumonia: serial high-resolution CT findings in 22 patients. AJR Am J Roentgenol. 2010;195(4):916-22.

Test Your Knowledge

A patient weighing 140kg is diagnosed with COP and the physician asks you for a prednisone dose recommendation, which dose do you recommend to start?

a. Prednisone 100mg daily
b. Prednisone 140mg daily
c. Prednisone 60mg daily
d. Prednisone 40mg daily

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c. **Prednisone 60mg daily**
d. Prednisone 40mg daily

Test Your Knowledge

True or False: All patients with COP must be treated with long-term/high dose steroids.

Test Your Knowledge

True or False: All patients with COP must be treated with long-term/high dose steroids.

FALSE

Questions

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