Antibiotic Update 2014: A Focus on Respiratory Infections

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Disclosures

- Speaker Bureau: Novartis, GSK, Sanofi-Pasteur, Merck, Takeda, Vivus
- Consultant: Vivus, Sanofi-Pasteur, Takeda

Objectives

- Upon completion of this lecture, the participant will be able to:
  1. Recognize the impact of antimicrobial resistance on infections encountered in a primary care setting.
  2. Discuss diagnostic criteria for ABRS, CAP and AECB.
  3. Identify latest treatment guidelines for the above conditions.

Pathogens and Resistance

Causative Pathogens in ABRS

- Streptococcus pneumoniae
- Haemophilus influenzae
- Moraxella catarrhalis

Prevalence of Respiratory Pathogens

http://cid.oxfordjournals.org/content/early/2012/03/20/cid.pr1043.full.pdf+html accessed 12-29-2012
**Streptococcus pneumoniae**

- Gram positive diplococci
- Most common cause of Community Acquired Pneumonia
  - Also the most common bacterial cause of OM and sinusitis
- 70% of children and 30% of adults have nasopharyngeal colonization
- Disease results from a microaspiration

**Mechanism for the Development of Antimicrobial Resistance**

- **Streptococcus pneumoniae**
  - Many mechanisms for resistance
  - Most common mechanism: Resistance from an alteration in the penicillin binding proteins which reduce/eliminate binding of penicillin to the proteins

**Streptococcus pneumoniae Resistance**

- Erythromycin resistance: ribosome modification and alteration in antibiotic transport
  - Of increasing concern is the ermAM gene. This gene confers cross-resistance to other 14, 15, and 16 membered rings (clarith, azith)

**Where are we now?**

- **S. pneumoniae**
  - 25% - 50% is not fully responsive to penicillin
  - 33% is resistant to macrolides

**Of Increasing Concern...**

- The first clinical isolate of **S. pneumoniae** to exhibit a high level of resistance to fluoroquinolones was found in 2001 in Taiwan
Streptococcus pneumoniae

- Most likely to be present with recurrent disease and least likely of all pathogens to resolve without treatment
- <30% chance of spontaneous resolution; Some sources say <10%

H. influenzae

- Gram negative coccosbacillus
  - Bronchotrachial tree becomes colonized and microaspiration occurs
- Most commonly seen among smokers, children of smokers and daycare children
  - 33% - 35% of H. influenzae is beta lactamase producing
  - TRUST results (Tracking Resistance in the United States)
    - 31.3% produced B lactamase in 99-2000
    - TMP-SMX resistance increased to 14% from 11.9%
    - Ampicillin resistance decreased from 33.9% to 30.7%

M. catarrhalis

- Gram negative bacillus
- Implicated in recurrent OM and Sinusitis
- Will often spontaneously resolve if left untreated
- 90% - 98% beta lactamase producing

Acute Bacterial Rhinosinusitis

Tammy

- 27 year old woman with an 12 day history of nasal discharge
- Seemed to be improving until past 2 days; developed worsening of post-nasal drip and pain over both cheeks. Temp past 1-2 days: 99.8 – 100.5
- Last antimicrobial use: 1 year ago
- PMH: Noncontributory; No tobacco, No allergies
- LMP: 2 weeks ago; denies pregnancy
- PE: Nasal mucosa erythematous. Maxillary sinuses 2+ tender

Remember...

- Secondary bacterial infection of the paranasal sinuses following a viral URI is relatively uncommon, estimated to be 0.5%-2% of adult cases and approximately 5% in children
- A national survey of antibiotic prescriptions for URI in the outpatient setting showed that antibiotics were prescribed for 81% of adults with acute rhinosinusitis despite the fact that approximately 70% of patients improve spontaneously in placebo-controlled randomized clinical trials

Pathophysiology of ABRS

- Normally, bacteria is removed from the sinuses by the mucous and the action of the cilia
- Ostia of a sinus becomes blocked
- Bacteria is normally present in the sinus
- Once the sinus opening is blocked, the bacteria is trapped and begins to grow in number

Predisposing Factors of ABRS

- Upper respiratory infections: Colds
- Allergy
- Smoking
- Anatomical abnormalities
- Immunodeficiency syndromes
- Dental infections

Diagnosis of Bacterial Acute Sinusitis

- Who should be treated with antimicrobial:
  - Persistent symptoms or signs compatible with acute rhinosinusitis, lasting for ≥10 days without any evidence of clinical improvement
  - Onset with severe symptoms or signs of high fever (≥39°C [102°F]) and purulent nasal discharge or facial pain lasting for at least 3–4 consecutive days at the beginning of illness
  - Onset with worsening symptoms or signs characterized by the new onset of fever, headache, or increase in nasal discharge following a typical viral upper respiratory infection (URI) that lasted 5–6 days and were initially improving (“double sickening”)

Diagnostic Testing

- Sinus X-rays
  - Allows visualization of the maxillary and frontal sinuses
  - Lack of specificity is a limiting factor
  - US Agency on Healthcare Policy – not cost effective
- CT Scan
  - Best visualization of the paranasal sinuses
  - Not recommended unless patient suspected to have supplicative complications

Normal sinuses


Sinus Disease

Cultures: What and When to Recommend

- Cultures should be obtained by direct sinus aspiration rather than by nasopharyngeal swab in patients with suspected sinus infection who have failed to respond to empiric antimicrobial therapy.
- Endoscopically guided cultures of the middle meatus may be considered as an alternative in adults, but their reliability in children has not been established.
- Nasopharyngeal cultures are unreliable and are not recommended for the microbiologic diagnosis of ABRS.

IDSA Clinical Practice Guideline for Acute Bacterial Rhinosinusitis in Children and Adults
Clinical Infectious Diseases Advance Access published March 20, 2012

Goals of Treatment

- Restore integrity and function of ostiomeatal complex
  - Reduce inflammation
  - Restore drainage
  - Eradicate bacterial infection

Treatment of Acute Bacterial Rhinosinusitis

- Nonpharmacologic Therapies
  - Cold steam vaporizer
  - Increased water intake
  - Intranasal saline irrigations with either physiologic or hypertonic saline are recommended as an adjunctive treatment in adults with ABRS.

Management Strategies in ABRS

- Antihistamines or decongestants
  - No longer recommended
- Topical corticosteroids
  - Intranasal corticosteroids are recommended as an adjunct to antibiotics in the empiric treatment of ABRS, primarily in patients with a history of allergic rhinitis.
- Corticosteroids
First line therapy
- Amoxicillin-clavulanate rather than amoxicillin alone is recommended as empiric antimicrobial therapy for ABRS in adults and children
- Standard dosage:
  - 500 mg/125 mg 1 pill po three times daily or....
  - 875mg/125mg 1 pill two times daily

Second line therapy
- Amoxicillin-clavulanate
  - 2000mg/125mg 1 pill two times daily or....
- Doxycycline
  - 100 mg 1 pill two times daily or 200 mg once daily

Individuals with β-lactam allergy
- Doxycycline
  - 100 mg 1 pill two times daily or 200 mg once daily or....
- Levofloxacin
  - 500 mg 1 pill once daily or....
- Moxifloxacin
  - 400 mg 1 pill once daily

What Constitutes at Risk for Resistance?
- Age < 2 years or > 65 years
- Daycare
- Antimicrobial within past 1 month
- Hospitalization within past 5 days
- Comorbidities
- Immunocompromised
High dose amoxicillin-clavulanate

- Anyone else qualify for high dose amoxicillin-clavulanate?
  - High-dose (2 g orally twice daily or 90 mg/kg/day orally twice daily) is recommended for children and adults with ABRS from geographic regions with high endemic rates (>10%) of invasive *S. pneumoniae*, those with severe infection (eg, evidence of systemic toxicity with fever of ≥39°C [≥102°F] or higher, and threat of supplicative complications)

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http://cid.oxfordjournals.org/content/early/2012/03/20/cid.cir1043.full.pdf+html
Accessed 12-29-2012
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Important Changes

- Macrolides (clarithromycin and azithromycin) are not recommended due to high rates of resistance among *S. pneumoniae* (30%)
- TMP/SMX is not recommended due to high rates of resistance among both *S. pneumoniae* and *H. influenzae* (30%–40%)
- Second and third-generation cephalosporins are no longer recommended due to variable rates of resistance among *S. pneumoniae*.

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http://cid.oxfordjournals.org/content/early/2012/03/20/cid.cir1043.full.pdf+html
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Summary: Antimicrobial Regimens in Adults

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<th>Duration of Therapy</th>
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<tr>
<td>Azithromycin</td>
<td>500 mg PO</td>
<td>1 dose</td>
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<tr>
<td>Levofloxacin</td>
<td>500 mg PO</td>
<td>5 days</td>
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Antimicrobial Regimens in Children

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Length of treatment

- The recommended duration of therapy for uncomplicated ABRS in adults is 5–7 days
- In children with ABRS, the longer treatment duration of 10–14 days is still recommended

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http://cid.oxfordjournals.org/content/early/2012/03/20/cid.cir1043.full.pdf+html
Accessed 12-29-2012
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When to Change Treatments

- An alternative treatment should be considered if symptoms worsen after 48–72 hours of initial empiric antimicrobial therapy, or when the individual fails to improve despite 3–5 days of antimicrobial therapy

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http://cid.oxfordjournals.org/content/early/2012/03/20/cid.cir1043.full.pdf+html
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Earl

- 56 year old man employed by the town presents with a 6 day history of a cough, worsening sob, fever, chills, pain in back with inspiration, and yellow-brown sputum.
  - PMH: Nonsmoker; quit 15 years ago
  - PE: Crackles in right lower lobe; Do not clear with coughing
  - X-ray: Consolidation-RLL
  - Sputum Gram Stain: Pending

Community Acquired Pneumonia

- Acute infection of the pulmonary parenchyma that is associated with symptoms of an infection such as fever, chills, shortness of breath and physical examination findings
  - Found in a person not hospitalized or residing in a long-term care facility for > 14 days before the onset of symptoms

Statistics: Community Acquired Pneumonia

- 915,900 episodes of CAP occur in adults 65 years of age each year in the United States
- Despite advances in antimicrobial therapy, rates of mortality due to pneumonia have not decreased significantly since penicillin became routinely available


Wright, 2014
Symptoms of Pneumonia

- Cough
- Fever
- Sputum production
- Shortness of breath
- Pleurisy
- Fatigue
- Malaise
- Anorexia

Signs

- Fever
- Tachypnea
- Tachycardia
- Crackles or decreased breath sounds
- Egophony, Bronchophony, Whispered Pectoriloquy
- Increased tactile fremitus
- Pleural rub

Most Common Outpatient Pathogens

- *Streptococcus pneumoniae*
- *Mycoplasma pneumoniae*
- *Haemophilus influenzae*
- *Chlamydia pneumoniae*
- Respiratory viruses


Earl

- 56 year old man employed by the town presents with a 6 day history of a cough, worsening sob, fever, chills, pain in back with inspiration, and yellow-brown sputum.
- PMH: Nonsmoker
- PE: Crackles in right lower lobe; Do not clear with coughing. RR – 20; Blood pressure – 110/76
- X-ray: Consolidation-RLL
- Sputum Gram Stain: Pending
- CBC: wbc 16,500; Bands 7%, Neuts: 73%

Most Important Decision!!!

- Decision to hospitalize or not
- Single most important decision in the course of the illness
  - Can determine life or death
  - Average mortality for hospitalized patients: 14% compared with non-hospitalized: <1%
- Average cost of treatment for CAP in the hospitalized patient vs. non-hospitalized
  - $7500 (20x more than non-hospitalized)

CURB-65 Score

- Confusion
- Urea > 7 mmol/L (BUN > 19 mg/dL)
- Respiratory rate ≥ 30/min
- Systolic blood pressure < 90 mm and Diastolic blood pressure ≤ 60 mm Hg
- Age ≥ 65 years of age

CURB-65 Score

- **CURB > 4** – ICU management
  - (27.8% 30-day mortality)
- **CURB = 3** – Hospital admission (consider ICU)
  - (14% 30-day mortality)
- **CURB = 2** – Hospital admission or outpatient management with very close follow-up
  - (6.8% 30-day mortality)
- **CURB = 0 – 1** – Outpatient management
  - (2.7% 30-day mortality)


Remember Earl...

- **Age**: 56
- **Confusion**: 0
- **Urea**: 0
- **Respiratory rate**: 0
- **Blood pressure**: 0
- **Age**: 0

CURB Score

- **outpatient**: 0 –


Diagnosis

- All patients suspected of pneumonia need to have a chest x-ray to confirm or establish the diagnosis
- Infectious Disease Society of America also recommends sputum for gram staining prior to initiating antibiotic therapy, particularly if you are going to be hospitalizing the individual


Please Remember...

- Four potential causes of a false negative chest x-ray
  - Early disease: Delay can be up to 10 days
  - Dehydration: Controversial but must be considered
  - Neutropenia: Unable to mount an inflammatory response
  - Pneumocystis Carinii: 10-40% of patients with this infection have a normal x-ray


Sputum Sample: To obtain or not?

- Prospective studies have failed to identify the cause of 40 - 60% of all CAP cases in the adult patient
  - However, *S. pneumoniae* is the most common cause of CAP
  - Responsible for approximately 2/3 of all cases of bacteremic pneumonia

[http://www.journals.uchicago.edu/CID/journal/issues/v44nS2/41620/41620.text.html accessed on 02-20-07](http://www.journals.uchicago.edu/CID/journal/issues/v44nS2/41620/41620.text.html)

IDSA/ATS 2007 Guidelines for CAP in Adults

- Practice Guidelines for the Management of Community-Acquired Pneumonia in Adults
  - Revised and published in Clinical Infectious Diseases 2007;44:S27 – S72

IDSA/ATS CAP Outpatient Treatment

• Classification
  – Previously healthy, no recent (within past 3 months) antibiotic use

• Likely causative pathogens
  – S. pneumoniae (Gm pos) with low DRSP risk
  – Atypical pathogens (M. pneumoniae, C. pneumoniae)
  – Respiratory virus including influenza A/B, RSV, adenovirus, parainfluenza

• Likely causative organism
  – S. pneumoniae (Gm pos) with DRSP risk
  – H. influenzae (Gm neg)
  – Atypical pathogens (M. pneumoniae, C. pneumoniae, Legionella)
  – Respiratory virus as mentioned above

• Classification
  – Comorbidities including: COPD, diabetes, renal or heart failure, asplenia, alcoholism, immunosuppressing conditions or use of immunosuppressing medications, malignancy or use of an antibiotic in past 3 months

IDSA / ATS 2007 Guidelines

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Previously Healthy and No Risks for DRSP</th>
<th>Previously Healthy and Recent Antibiotics</th>
<th>Comorbidities and No Recent Antibiotics</th>
<th>Comorbidities and Recent Antibiotics</th>
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<tbody>
<tr>
<td>Antibiotic Options</td>
<td>Strong: Macrolide</td>
<td>Respiratory Quinolone</td>
<td>Respiratory Quinolone</td>
<td>Respiratory Fluoroquinolone</td>
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<tr>
<td>Antibiotic Options</td>
<td>Weaker: Doxycycline</td>
<td>Macrolide + High dose amoxicillin</td>
<td>Macrolide + Beta Lactam</td>
<td>Advanced Macrolide plus beta lactam</td>
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<tr>
<td>Antibiotic Options</td>
<td></td>
<td>Macrolide + High dose amoxicillin/clav</td>
<td></td>
<td>***&gt; 20% of infection with high level Macrolide resistance - Quinolone</td>
</tr>
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Wright, 2014
Continuing With Earl

- 56 year old man employed by the town presents with a 6 day history of a cough, worsening sob, fever, chills, pain in back with inspiration, and yellow-brown sputum.
  - PMH: Nonsmoker
  - PE: Crackles in right lower lobe; Do not clear with coughing. RR - 20
  - X-ray: Consolidation-RLL
  - Sputum Gram Stain: Pending
  - CBC: wbc 16, 5000; Bands 7%, Neuts: 73%

Treated With...

- Macrolide x 5 days
- Clinical improvement within 48 hours
- Chest x-ray: who should be repeated?
  - Newer guidelines don't address this issue
  - Older guidelines say 6 – 12 weeks after treatment
  - Guidelines in other countries:
    - Increased risk of cancer: > 50 years of age and/or smoker

Length of Therapy

- Shortened to 5 days
- Provided that the patient is afebrile by 48 – 72 hours

Bronchitis

- Definition: Inflammatory condition of the tracheobronchial tree
  - Acute bronchitis
    - Most cases of acute bronchitis are viral (90-95%)
  - Chronic bronchitis

COPD = chronic obstructive pulmonary disease; AECB = acute exacerbations of chronic bronchitis;
Disease Burden

- 16 million people in the U.S. have COPD
- 110,000 deaths annually
- Prevalence and mortality are increasing as population ages
- 14 million COPD patients have chronic bronchitis (median of 3 exacerbations per year)

Risk Factors for Chronic Bronchitis

- Women > Men
- Hereditary factors (α-1-antitrypsin)
- Occupational exposure
- Cigarette smoking (90% of all cases)
- Air pollution
- Childhood respiratory infection

Role of Cigarette Smoking

- In the U.S., up to 90% of chronic bronchitis is related to tobacco smoke exposure
- Smokers are more likely than nonsmokers to die of COPD
- Persistent inflammation in the airway and in the parenchyma is present in ex-smokers
- Loss of lung function at an accelerated rate may continue in ex-smokers with established COPD
- FEV₁ decline equivalent in ex-smokers and active smokers (65 mL/y vs. 69 mL/y)

Risk Factors for Chronic Bronchitis

- Air Pollution
- Occupational Exposure
- Childhood Respiratory Infection
- Women > Men
- Hereditary Factors (α-1-antitrypsin)
- Cigarette Smoking (90% of all cases)

Importance of These Events

- We now recognize ABECB as clinically important events in the patient with COPD
- Believed that inadequate treatment of ABECB can worsen the underlying COPD

Bronchiectasis

Chronic Bronchitis
- Chronic productive cough for 3 months in each of 2 successive years
- > 80% of COPD

Emphysema

AECB
- Increased dyspnea
- Increased sputum volume
- Increased sputum purulence

AECB: Acute bacterial exacerbation of chronic bronchitis


Wright, 2014
The Role of Bacteria in Chronic Bronchitis: The “Vicious Circle” Theory

Bacterial colonization, associated inflammatory response, and alteration of host defenses

↓ Ciliary function, mucus production, airway mucosal damage
↓ Progression of chronic bronchitis
↓ Mucociliary clearance of microorganisms

Cigarette Smoking

Airway epithelial injury

Effective antibiotic therapy helps break the “vicious circle”

Economic Impact of AECB

• Treatment sought for >90% of acute exacerbations (1994)
• >$1.5 billion in direct healthcare costs for AECB
• Majority of costs were for hospitalizations
• Therapy allowing patients to be treated in the outpatient setting would significantly reduce costs

Criteria for Diagnosis

• Chronic bronchitis
• Plus:

AECB Diagnostic Clues

• Increased
  – Dyspnea*
  – Sputum volume*
  – Sputum purulence*
  – Cough
• Chest tightness
• Fluid retention
• Wheeze
• Decrease in airflow
• Fatigue or not feeling well

* The three cardinal symptoms of AECB

Diagnosis May Include

• History
• Physical examination
• Laboratory
  – CBC with differential
• Additional testing
  – PFT’s
  – Sputum sample
  – Chest x-ray
  – ABG’s, if hospitalized
Etiology and Role of Bacteria

Causes of AECB

- Result of a virus in 25 – 50% of the cases
- Role of bacteria in ABECB remains controversial
  - *S. pneumoniae*
  - *H. influenzae*
  - *M. catarrhalis*
- All are isolated from tracheobronchial tree between acute exacerbations

Bacterial Etiology of AECB

- *H. influenzae* 49%
- *S. pneumoniae* 19%
- *M. catarrhalis* 14%
- Other 18%

- *H. influenzae* is the most common isolate
- *Streptococcus pneumoniae* and *Moraxella catarrhalis* are also common
- *Mycoplasma pneumoniae* and *Chlamydia pneumoniae* are rarely documented

Mechanisms Facilitating *H. influenzae* Infection in Smokers

- Nicotine directly stimulates the growth of *H. influenzae*
  - *H. influenzae* requires NAD⁺ in order to grow
  - Nicotine provides a substrate for the generation of NAD⁺
- *H. influenzae* releases factors that are ciliotoxic, resulting in
  - Decline in ciliary activity
  - Damage to the respiratory epithelium

Prevalence of β-Lactam Resistance in *H. influenzae* and *M. catarrhalis*

- The presence of the β-lactamase inhibitor clavulane extends antibiotic activity

Diagnosis

- Assess spirometry, if able
- O2 saturation of < 90% may indicate respiratory failure
- Chest x-ray
  - Consider if fever is present or low O2 saturation

Adapted from www.goldcopd.org accessed 12-29-2012
Who Should Receive Antimicrobials?

- Individuals with 3 cardinal symptoms of COPD
  - Increased dyspnea
  - Increased sputum volume
  - Increased sputum purulence
- Individuals with 2 cardinal symptoms of COPD if one of the symptoms is:
  - Increased purulence of sputum
- Individuals requiring hospitalization

Adapted from www.goldcopd.org accessed 12-29-2012

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<table>
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<tr>
<th>Group A</th>
<th>Likely pathogens</th>
<th>Recommended ABX</th>
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<tbody>
<tr>
<td>Mild exacerbation</td>
<td>Gram-positive</td>
<td>PCN</td>
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<tr>
<td>No risk factors for poor outcome</td>
<td>Gram-negative</td>
<td>Amoxicillin</td>
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<tr>
<td>Comorbidities</td>
<td>H. influenzae</td>
<td>Tetracycline</td>
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<tr>
<td>Severe COPD</td>
<td>M. catarrhalis</td>
<td>TMP/SMX</td>
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<tr>
<td>Frequent exacerbations</td>
<td>Viruses</td>
<td>Second option</td>
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<tr>
<td>Antimicrobial use within past 3 months</td>
<td>Atypical pathogens</td>
<td>Amox/Clav</td>
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<tr>
<td>C. Pneumoniae</td>
<td>DRSP</td>
<td>Azithromycin</td>
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<td>Moderate exacerbation</td>
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Additional Pharmacologic Treatments

- Corticosteroids
  - If FEV 1 < 50% of predicted: 30 - 40 mg prednisone per day for 7 - 10 days
- Inhaled Beta-2 agonist
  - Consider anticholinergic, if not already using
- Cough suppressants
- Oxygen therapy

Adapted from www.goldcopd.org accessed 12-29-2012

Additional Nonpharmacologic Treatments

- Smoking cessation
- Immunizations:
  - Yearly influenza
  - Pneumococcal vaccination
- Increased water intake
- Good nutrition
- Avoidance of pollutions

Adapted from www.goldcopd.org accessed 12-29-2012
Additional Considerations

- 10 – 30% of individuals with AECB will not respond to standard therapies
- Consider additional differential diagnoses
  - Pneumonia
  - Pneumothorax
  - Pleural Effusion
  - Pulmonary Embolism

Adapted from www.goldcopd.org accessed 12-29-2012

Hospitalization

- The following patients should be considered for hospitalizations
  - Marked increase in intensity of symptoms
  - Severe COPD
  - Onset of new physical signs (i.e. cyanosis)
  - Failure of exacerbation to respond to initial treatments
  - Significant comorbidities
  - Newly occurring dysrhythmias
  - Older age
  - Insufficient home assistance

Adapted from www.goldcopd.org accessed 12-29-2012

End of Presentation!

Thank you for your time and attention.

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