Acute Exacerbations of Chronic Bronchitis

Therapeutics/PHMPR-732

John A. Bosso, Pharm.D.

Chronic Obstructive Pulmonary Disease

- Characterized by fixed obstruction of airways caused by chronic bronchitis, emphysema, or both
- Affects ≥ 14.2 million in USA
- Accounts of 16 million physician visits and 500,000 hospitalizations/yr
- 4th leading cause of death in USA
  - Mortality rates are rising
- Cost for COPD in 2001: $30.4 billion

2. Stoller. NEJM 2002;346:988-94

Acute Bronchitis, Chronic Bronchitis, and Acute Exacerbation of Chronic Bronchitis

- Acute Bronchitis
  - Short-term cough, producing mucoid sputum
  - Usually self-limited viral infection
- Chronic Bronchitis
  - Productive cough ≥ 3 months in 2 consecutive years
  - Comprises ~85% of COPD (emphysema ~15%)
- Acute Exacerbation of Chronic Bronchitis (AECB)
  - Increase in dyspnea or sputum purulence/volume in a patient with chronic bronchitis
  - Often bacterial (ABECB)

COPD=Chronic Obstructive Pulmonary Disease.


Chronic Bronchitis

- Clinical course: chronic disability with intermittent acute exacerbations
  - Excessive cough and sputum production on most days for at least 3 mo during at least 2 consecutive yrs
- Acute exacerbations (AECB)
  - Manifested as ↑ dyspnea, sputum volume, and/or sputum purulence
  - The average patient has 3 exacerbations/yr usually during the winter months
Acute Exacerbations of Chronic Bronchitis (AECB): Epidemiology

- COPD comprises a spectrum of airway diseases
- Smoking is most common cause of COPD
- COPD is 4th leading cause of death in US
- FEV₁ <50% predicted value associated with reduced 5-year survival
- A significant proportion of COPD patients have frequent and recurring AECB
- Role of bacterial infection in AECB is debated but is considered a leading cause

Risk Factors for Chronic Bronchitis

- Cigarette Smoke
- Pollutants
- Genetic Predisposition
  - Atopic Disease
  - Alpha₁-antitrypsin deficiency

Diagnosis of ABECB

- Diagnosis and classification based on
  - Patient history
  - Cardinal symptoms
- Radiography
  - Useful in hospitalized/ER patients
  - Not as useful in ambulatory patients
- Bronchoscopy effective, but not routinely performed
- Microbiology testing identifies the pathogen only in a minority of cases (16%–40%)

Classification of AECB - 1

- Type 1
  - Increased dyspnea
  - Increased sputum volume
  - Increased sputum purulence
- Type 2
  - 2 of the above symptoms
- Type 3
  - 1 of the above symptoms


**Classification of AECB - 2**

- **Uncomplicated**
  - ≤ 3 exacerbations/yr
  - No comorbid illness
  - FEV₁ > 50% predicted
- **Complicated**
  - > 3 exacerbations/yr
  - Serious comorbid illness or FEV₁ < 50% predicted
- **Complicated/at risk for P. aeruginosa**
  - Bronchiectasis
  - Chronic corticosteroid use
  - Frequent antibiotic therapy
  - FEV₁ < 35% predicted


**Bacterial Pathogens in AECB**

- *Haemophilus influenzae*
- *Streptococcus pneumoniae*
- *Moraxella catarrhalis*
- **Other**
  - *S. aureus*
  - *P. aeruginosa*
  - Atypical pathogens


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**AECB Etiology: Colonizer to Pathogen**

The cycle from colonizer to pathogen

Adapted from Wilson, 1995.

**Bacterial Pathogens in Different Populations**

- Core pathogens, most common pathogens in mild exacerbations of COPD: *H. influenzae, S. pneumoniae, M. catarrhalis*
- With exacerbations, numbers of organisms increase
- Greater frequency of noncore pathogens with more severe exacerbations
Bacterial Pathogens in Severe AECB

- \textit{S. pneumoniae}
- \textit{H. influenzae}
- \textit{M. catarrhalis}
- Gram-negative enteric bacilli (emergence posttreatment)
- \textit{P. aeruginosa} (persistence posttreatment)

Frequently drug-resistant

Adapted from Soler et al, 1998; Anzueto et al, 1998.

AECB: Distribution of Bacteria According to Lung Function

Probable Pathogens by Patient Group

- Uncomplicated AECB
  - \textit{S. pneumoniae}, \textit{H. influenzae}, \textit{M. catarrhalis}, \textit{H. parainfluenzae}
- Complicated AECB
- Complicated AECB/PA


New Strains of Bacteria Associated With Exacerbations

- Conducted bacterial molecular typing of sputum samples during 56 months of 81 COPD patients
- In samples collected during an exacerbation:
  - 33\% contained a new strain
  - 15.4\% did not (\(P<.001\))
- Isolation of a new strain of \textit{H. influenzae}, \textit{M. catarrhalis}, or \textit{S. pneumoniae} was associated with a significantly increased risk of an exacerbation
- Supports causative role of bacteria in exacerbations

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Burden of Disease:
High-Risk for AECB Mortality

- Advanced age (>65 years old)
- Severity of impairment of lung function
- Development and severity of nonrespiratory dysfunction


Considerations When Treating AECB

- Role of bacterial infection
- Spontaneous resolution of exacerbations
- More rapid resolution of infection and decreased treatment failures
- Role of antimicrobials in preventing or slowing the decline in respiratory tract function


Therapeutic Considerations of AECB

- Prevention
  - Cessation of smoking
  - Vaccination (yearly influenza, pneumococcal)
- Empiric antimicrobial therapy to cover the following:
  - Beta-lactamase production (H. influenzae, M. catarrhalis)
  - Multidrug-resistant S. pneumoniae in at-risk patients
- Patient factors
  - >4 exacerbations/year
  - Significant comorbidity, lung dysfunction, age >65


Pharmacotherapy

- Bronchodilators
  - ß-agonists, anticholenergics
- Systemic corticosteroids
  - 2 weeks duration
  - Inhaled steroids modest short-term benefit
- Antibiotics
- Supplemental O₂
  - ± noninvasive mechanical ventilation
Guidelines for Treatment of AECB

- VHA
  - Guidelines synthesis: COPD, Pt. II
    - (http://www.guideline.gov)
- ACP/ASIM/ACCP
- Global Initiative for Chronic Obstructive Lung Disease (GOLD) WHO-NIH
  - Panwels et al. Am J Respir Crit Care Med 2001;164:1256-76.

Role of Antibiotic Therapy for AECB

- Indicated for Type 1 and 2 exacerbations
  - consider for those with comorbidities (diabetes, CAD) or airway obstruction
- Improves clinical outcome
- Decreases frequency of recurrent exacerbations
- Reduces burden of colonized pathogens
- Prevention of more severe infections (pneumonia)
- Slows progression of lung injury

Antibiotic Therapy for AECB
Immediate, Short-term Benefits

- Reduction of duration of symptoms, leading to a higher rate of clinical cure and a lower rate of clinical deterioration
- Prevention of progression to pneumonia
- Avoidance of hospitalization
- Early return to work

Patients Likely to Benefit from Antibiotic Therapy

- Patients with ≥3 exacerbations in past year
- Patients with Type 1 or 2 exacerbations
- Patients with comorbidities
  - asthma, CAD, diabetes
- Marked airway obstruction

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Antimicrobials to Treat ABECB

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>H. influenzae</th>
<th>S. pneumoniae</th>
<th>P. aerug</th>
<th>K. pneum</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>β+</td>
<td>β−</td>
<td>P-NS</td>
<td>P-S</td>
</tr>
<tr>
<td>Amoxicillin</td>
<td>−</td>
<td>+</td>
<td>−</td>
<td>+</td>
</tr>
<tr>
<td>Amox/clav</td>
<td>+</td>
<td>+</td>
<td>+/−</td>
<td>++</td>
</tr>
<tr>
<td>Azithromycin</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>−</td>
</tr>
<tr>
<td>Cefuroxime</td>
<td>+/−</td>
<td>+/−</td>
<td>−</td>
<td>+</td>
</tr>
<tr>
<td>TMP/SMX</td>
<td>++</td>
<td>++</td>
<td>−</td>
<td>+</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>++</td>
<td>++</td>
<td>+/−</td>
<td>++</td>
</tr>
<tr>
<td>Levofloxacin</td>
<td>++</td>
<td>++</td>
<td>+</td>
<td>+</td>
</tr>
</tbody>
</table>


Susceptibility Rates (%) Among ABECB Isolates (RESP Study)

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>H. influenzae</th>
<th>M. catarrhalis</th>
<th>S. pneumoniae</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ND</td>
<td>85</td>
<td>63</td>
</tr>
<tr>
<td>Erythromycin</td>
<td>99</td>
<td>99</td>
<td>76</td>
</tr>
<tr>
<td>Tetracycline</td>
<td>97</td>
<td>99</td>
<td>ND</td>
</tr>
<tr>
<td>Cefuroxime</td>
<td>100</td>
<td>100</td>
<td>95</td>
</tr>
<tr>
<td>Amox/clav</td>
<td>100</td>
<td>100</td>
<td>ND</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>100</td>
<td>100</td>
<td>99</td>
</tr>
<tr>
<td>Gatifloxacin</td>
<td>100</td>
<td>100</td>
<td>99</td>
</tr>
</tbody>
</table>

RESP=Respiratory Surveillance Program.
PRSP=Penicillin-resistant S. pneumoniae (MIC ≥ 2.0 μg/mL).
β-Lactams: CLSI nonmeningitis breakpoints.

S. pneumoniae Antimicrobial Resistance
TRUST 10 (2006)

S. pneumoniae
Penicillin Resistance
(Resistant, MIC ≥ 2 µg/mL)

National Rate:
Penicillin = 14.1% R

S. pneumoniae
Azithromycin Resistance
(Resistant, MIC ≥ 1 µg/mL)

National Rate:
Azithromycin = 20.3% R
Erythromycin = 31.3% R

PRSP*: Reduced Susceptibilities to β-Lactams and Macrolides:
TRUST 10 (2006), N=426

In vitro activity does not necessarily correlate with clinical results.
*PRSP = penicillin-resistant S. pneumoniae (MIC ≥ 2.0 µg/mL), ceftriaxone and amox/clav %S based on CLSI nonmeningitis breakpoints.

Data on file, Ortho-McNeil, Inc.
Summary of *H. influenzae* and *M. catarrhalis* Isolates: TRUST 10 (2006)

- *H. influenzae* (n = 727)
  - Resistance to ampicillin (28.6%) and TMP/SMX (18.6%)
  - Stable resistance pattern (2001-2006)
  - No resistance to levofloxacin (100% S in 2005, 2006)
- *M. catarrhalis* (n = 780, TRUST 8, 2004)
  - β-lactamase positive: 94.5%
  - No change in MIC over 8 yrs (1996-2004)
  - Not tested in TRUST 9 or 10
  - No resistance to levofloxacin (100% S)

*In vitro activity does not necessarily correlate with clinical results.*

Data on file, Ortho-McNeil, Inc.

Antibiotic Treatment of AECB Based on Clinical Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Group 1 (Uncomplicated)</th>
<th>Group 2* (Complicated)</th>
<th>Group 3† (Pseudomonas)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amox-Clav</td>
<td>■</td>
<td>■</td>
<td>■</td>
</tr>
<tr>
<td>Cephalosporin</td>
<td>■</td>
<td>■</td>
<td>■</td>
</tr>
<tr>
<td>Doxycycline</td>
<td>■</td>
<td>■</td>
<td>■</td>
</tr>
<tr>
<td>Macrolide</td>
<td>■</td>
<td>■</td>
<td>■</td>
</tr>
<tr>
<td>Newer quinolone</td>
<td>■</td>
<td>■</td>
<td>■</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>■</td>
<td>■</td>
<td>■</td>
</tr>
</tbody>
</table>

*Older with recurrent exacerbations and significantly reduced FEV1.
†Complicated with comorbid conditions or steroids.


Antibiotic Therapies for AECB According to Patient Subsets

- **Uncomplicated**
  - Macrolide (azithro or clari) or newer ceph, or doxy

- **Complicated**
  - Fluoroquinolone or amox/clav (or IV β-lactam if hospitalized)*

- **Complicated/risk for PA**
  - Fluoroquinolone with antipseudomonal activity**

*complicated AECB with only 1 risk factor could be txd with azithromycin
**consider dual antipseudomonal therapy if hospitalized, cipro 750 PO bid


Rationale for Abbreviated Therapy

- Standard duration of treatment for AECB is 7 to 10 days
  - However, rapid bacterial killing and/or post-antibiotic effects may allow for shorter treatment courses
- Potential advantages of shorter duration of treatment
  - Increased compliance
  - Decreased costs
  - Decreased adverse events
  - Decreased incidence of antibiotic resistance

**Efficacy of Abbreviated Therapy in AECB**

<table>
<thead>
<tr>
<th>Agent (Dose)</th>
<th>CR (post-tx) n/N(%)</th>
<th>CR (follow-up) n/N(%)</th>
<th>BR (post-tx) n/N(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>DeAbate et al. (2000)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AZI (500 qdX5d)</td>
<td>127/135(94)</td>
<td>127/135(94)</td>
<td>127/135(94)</td>
</tr>
<tr>
<td>MOX (400 qdX10d)</td>
<td>136/144(90)</td>
<td>134/140(96)</td>
<td>135/140(91)</td>
</tr>
<tr>
<td>CLA (500 bidX10d)</td>
<td>121/123(96)</td>
<td>118/123(96)</td>
<td>110/120(91)</td>
</tr>
<tr>
<td>Day 0-6</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Day 30</td>
<td>48/62(77)</td>
<td>40/61(66)</td>
<td>26/60(43)</td>
</tr>
<tr>
<td>Day 12-16</td>
<td></td>
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</tbody>
</table>

**Which AECB Patients Are More Prone to Therapeutic Failure?**

- Older age (> 65 yoa)
- Severe underlying COPD (FEV<sub>1</sub> < 35%)
- Comorbid cardiopulmonary disease
- Four acute exacerbations of chronic bronchitis in 12 months
- Severe symptoms at presentation
- Prolonged Hx of COPD (> 10 yrs)

**Antibiotic Therapy for Acute Bronchitis Without Underlying Chronic Bronchitis**

- Antibiotics are not appropriate for uncomplicated acute bronchitis without underlying lung disease
- When patients with a history of COPD are excluded:
  - Antibiotics = placebo
  - Azithromycin = vitamin C
- However, antibiotics are significantly more effective than placebo in patients with acute bacterial exacerbation of chronic bronchitis

**References**