RESISTANCE

TO PRESCRIBE OR NOT: DIFFERENTIATING THE NEED FOR ANTIMICROBIALS IN RTIS

FROM THE EDITORS' DESK

Antimicrobial resistance is a significant problem in today's healthcare environment. Reports have predominantly targeted the hospital environment as the main source of resistant infections, such as those caused by methicillin-resistant *Staphylococcus aureus* (MRSA) "superbugs." Resistant hospital-acquired infections are associated with substantial morbidity, mortality, and costs. This has led to the movement towards increased transparency and reduction in reimbursement for such "preventable" conditions.¹

What is important to note is that the concerns pertaining to antimicrobial resistance are just as important in the outpatient setting. The call for more judicious use of antimicrobials in the primary care setting began in the 1990s when resistance rates of *Streptococcus pneumoniae* to penicillin and the macrolides were rapidly increasing.² This was associated with a gradual reduction in the number of prescriptions by primary care physicians (PCPs) to treat upper respiratory tract infections (RTIs) in Europe.^{3, 4} However, this trend has not been as obvious in the United States.

- In 1998, acute RTIs were associated with over 76 million office visits resulting in 41 million antimicrobial prescriptions–55% (22.6 million) of these prescriptions were considered unnecessary since the RTIs were likely caused by viral pathogens.⁵
- According to a 2006 study that included 52,135 RTI-associated office visits, the percentage of patients receiving antimicrobials remains high despite that only 5%–25% of these patients may actually have a bacterial infection.⁶

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ON THE FRONTLINE OF CARE

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(From The Editor's Desk...)

Patients (%) receiving antimicrobial prescriptions for RTIs, 1998-2003				
All URIs	65.0%			
Acute Sinusitis	81.3%			
Acute Bronchitis	75.7%			
Acute Pharyngitis	65.0%			
Nonspecific URI	33.4%			

The overuse of antimicrobials has several potential consequences, including increasing the risk of resistance development and the probability of an adverse event or drug–drug interaction while inflating overall healthcare costs. Given the number of antimicrobial prescriptions for RTIs written by PCPs, this sector of healthcare can make a major impact in reducing or minimizing resistance development in the community. Education on the proper use and selection of antimicrobials for community-acquired RTIs is imperative in reducing unnecessary antimicrobial use and, thus, minimizing the selective pressure for resistance.

This bulletin, therefore, focuses on

- When an antimicrobial is appropriate for patients who present with an RTI
- How to select the appropriate agent when a bacterial infection is suspected

This bulletin discusses lower RTIs as these are associated with more serious complications and have a greater risk of mortality. Future bulletins will discuss the impact of resistance in the community on antimicrobial selection and will offer insights on how to appropriately select and dose these agents to achieve successful clinical outcomes while minimizing the risk of resistance development.

CME ACCREDITATION

RELEASE DATE September 9, 2009 EXPIRATION DATE September 9, 2010

TARGET AUDIENCE

This educational initiative has been designed to meet the needs of physicians and other healthcare professionals involved in the diagnosis, management, and treatment of outpatients with RTIs.

PURPOSE STATEMENT

The purpose of this activity is to educate primary care physicians and other healthcare professionals on when an antimicrobial agent is needed to treat an RTI, identifying the risk factors for a resistant RTI, and optimizing antimicrobial therapy. With this knowledge, healthcare professionals involved in the diagnosis, management and treatment of outpatients with RTIs will be able to tailor therapy to achieve successful outcomes.

LEARNING OBJECTIVES

At the conclusion of this activity, learners should be able to

• Determine when an antimicrobial agent is needed to treat a respiratory tract infection (RTI)

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ACCREDITATION **Physicians**

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- Advisory Boards: Optimer, Targanta, Astellas, and Novartis.
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The off-label use of any antimicrobial agent is not discussed during this activity.

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FEE

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ACUTE BRONCHITIS

Acute bronchitis is among the most common causes of visits to PCPs. Data from the National Health Interview Survey indicate that 4% to 5% of the adult population will have at least one episode each year.⁷ This was confirmed in a more recent study involving Oregon Medicaid patients in which approximately 5% of the population was diagnosed with acute bronchitis each year.⁸

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The primary symptom of acute bronchitis is cough lasting 21 days or less in otherwise healthy patients.⁹ (*Please note* that cough lasting longer than 21 days should be considered "chronic" or "persistent" and must be managed differently.) Before proceeding with the management of these patients, it is important to rule out other causes of cough, such as asthma and pneumonia.

It is important to recognize that in 90%-95% of patients, acute bronchitis is due to a viral pathogen (**Table 1**).⁹ Less than 10% of patients with acute bronchitis have a bacterial cause of infection and only a few bacteria have been identified as potential causative pathogens.^{10, 11} A small proportion of patients may also have non-infectious disease causes–occult asthma and allergic or occupational exposures.⁹ In the 90%-95% of patients with viral acute bronchitis, antimicrobials are not recommended.⁹ However, studies have shown 50%-80% antimicrobial prescription rates.^{8, 12} Systematic reviews and meta-analyses prove no consistent effect of antimicrobials on the duration or severity of illness in these patients.^{13, 14}

Antimicrobials are appropriate in

- Patients suspected with pertussis infection– those exposed to a known pertussis infection or symptomatic patients during a documented pertussis epidemic.⁹
- Patients during mycoplasma or *C. pneumoniae* outbreaks⁹

When managing patients with acute bronchitis, it may be useful to refer to the illness as a "chest cold". This will help discourage the perception that antimicrobial therapy is needed. Inhaled bronchodilators may be prescribed in some circumstances to help relieve symptoms while increase in fluid intake should be encouraged.⁹ For those experiencing persistent irritative cough, a trial of a scopolamine-containing product should be considered.

/iral Pathogens (90%-95% of cases)³	Bacterial Pathogens (<10% of cases) ^{10, 11}
Influenza	Bordetella pertussis
Parainfluenza	Mycoplasma pneumoniae
Respiratory syncitial virus (RSV)	Chlamydophila pneumoniae
Coronavirus	
Adenovirus	
Rhinoviruses	

Table 1. Common causative pathogens of acute bronchitis

ACUTE EXACERBATION OF CHRONIC BRONCHITIS (AECB)

Chronic bronchitis (defined as cough with sputum production for most days of at least 3 months a year for two consecutive years) is present in approximately 85% of the patients with chronic obstructive pulmonary disease (COPD).¹⁵ It can also occur in the absence of airway obstruction and therefore it is not always associated with COPD.

Defining AECB is difficult given the lack of standardized physiological, laboratory, or radiological diagnostic tests for this condition and its definition in clinical practice is varied. However, it typically involves the three cardinal criteria first established by Anthonisen and colleagues in 1987–increased sputum volume, increased sputum purulence, and increased dyspnea (**Table 2**).¹⁶ Based on these criteria, a COPD patient typically has 2 to 3 exacerbations each year. These criteria have also been used in the Canadian guidelines on AECB management to stratify patients into 3 categories–Type 1 (severe exacerbation), Type 2 (moderate exacerbation), and Type 3 (mild exacerbation) (**Table 2**).

Table 2. AECB criteria and stratification

1. Increased sputum volume

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- 2. Increased sputum purulence
- 3. Increased dyspnea

AECB Stratification based on Canadian guidelines for the management of AECB¹⁵

Type 1 (severe exacerbation)	All three symptoms present
Type 2 (moderate exacerbation)	Two symptoms present
Type 3 (mild exacerbation)	At least one of the symptoms present + one of the following:
	 Upper RTI in previous 5 days Increased cough and wheezing Increased respiratory or heart rate (20% above baseline) Fever

ETIOLOGY OF AECB

80% of all AECB episodes are due to viral/bacterial infections (30% due to viral and 50% due to bacterial) and only 20% are due to environmental exposure **(Table 3)**. Antimicrobial therapy should only be considered when a bacterial infection is responsible for the AECB episode. The therapy itself depends on the specific pathogen suspected.

Infectious Disease (80% of all episodes)¹⁷ **Viral Infections Bacterial Infections** • 30% of all AECB episodes 50% of all AECB episodes **Optimal Management Bacterial Etiology** Strategy • Aerobic gram-positive and gram-negative pathogens No antimicrobial therapy (40%-50% of episodes) - Patients with well-preserved lung function: Haemophilus influenzae, Moraxella catarrhalis, and Streptococcus pneumoniae - More severely ill patients with declining lung function: H. influenzae, M. catarrhalis, and S. pneumoniae + Pseudomonas aeruginosa and Enterobacteriaceae • Atypical pathogens, primarily *C. pneumoniae* (<10% of episodes) **Optimal Management Strategy** Antimicrobial therapy based on the pathogen Non-Infectious Disease (20% of all episodes)

Table 3. Causes of AECB

Environmental Exposure

- Tobacco smoke
- Dust
- Allergens
- Pollutants

Optimal Management Strategy

- Treat the allergy
- Encourage eliminating exposure to tobacco smoke (though this can be challenging for many patients)

APPROPRIATE USE OF ANTIMICROBIALS FOR AECB

Early studies on the use of antimicrobials for the treatment of AECB showed little benefit when compared with placebo.^{18, 19} However, when patients were categorized by type of symptoms, studies were able to identify those who were more likely to benefit from antimicrobial treatment.

In a randomized, double-blind study, Anthonisen and colleagues divided patients into Type 1, Type 2, and Type 3 (based on the Canadian guidelines) and compared success rates for those receiving antimicrobials (trimethoprim/sulfamethoxazole, amoxicillin, or doxycycline) versus placebo.¹⁶

- Overall success rates were 55% in the placebo group and 68% in the antimicrobial group.
- Results stratified by type of exacerbation
 - Differences in success rate between antimicrobial and placebo groups were greatest in patients with Type 1 (severe exacerbation), while the differences were less obvious for Type 2 (moderate exacerbation) and Type 3 (mild exacerbation) (Figure 1).
 - The rate of deterioration was double in Type 1 patients receiving placebo versus those receiving antimicrobials (30.5% versus 14.3%).

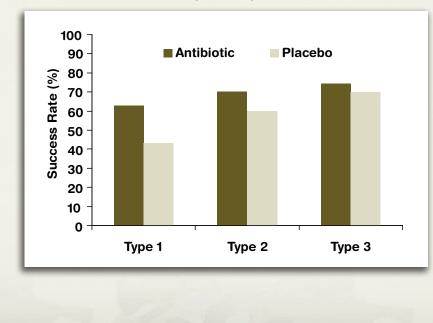


Figure 1. Success rates among patients with AECB stratified by severity¹⁶

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Patient stratification has become an important input in deciding when an antimicrobial is necessary for managing AECB. The Canadian Thoracic Society (CTS) and the Canadian Infectious Diseases Society (CIDS) offer guidelines on how to stratify patients having a "Type 1" exacerbation to which antimicrobial should be selected (**Table 4**).¹⁵

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Risk Group	Basic Clinical State	Symptoms and Risk Factors	Antimicrobial Needed?	Rationale
0	Acute tracheobronchitis	Cough and sputum without previous pulmonary disease	Νο	These patients typically have a viral infection and would not require an antimicrobial unless symptoms persist for more than 10-14 days.
1	Chronic bronchitis without risk factors (simple)	Increased cough and sputum, sputum purulence, and increased dyspnea	Yes	These patients are likely to be infected with a common respiratory tract pathogen- <i>H.</i> <i>influenzae, M.</i> <i>catarrhalis,</i> or <i>S. pneumoniae.</i>
II	Chronic bronchitis with risk factors (complicated)	As in Group I + One of the following: - FEV ₁ <50% predicted - >4 exacerbations per year - Cardiac disease - Use of home oxygen - Chronic oral steroid use - Antimicrobial use in the past 3 months	Yes	These patients are more likely to be infected with an Enterobacteriaceae (such as <i>Klebsiella</i> <i>pneumoniae</i>) or <i>P. aeruginosa</i> , and multidrug resistance may also be a concern, particularly if there is a history of recent prior antimicrobial use. These patients may require referral to a specialist or hospital and treatment should be tailored to the specific pathogen.
	Chronic suppurative bronchitis	As in Group II with constant purulent sputum - Some have bronchiectasis - FEV ₁ <35% predicted - Multiple risk factors (eg, frequent exacerbations and FEV ₁ <50% predicted)	Yes	These patients are more likely to be infected with an Enterobacteriaceae (such as <i>Klebsiella</i> <i>pneumoniae</i>) or <i>P. aeruginosa</i> , and multidrug resistance may also be a concern, particularly if there is a history of recent prior antimicrobial use. These patients may require referral to a specialist or hospital and treatment should be tailored to the specific pathogen.

Table 4. Stratification of patients with AECB and suggested management approach¹⁵



CAP is a leading cause of morbidity and mortality in the United States associated with nearly 6 million cases each year and approximately 1.5 million hospitalizations^{20, 21}–1 million of these cases are attributed to those \geq 65 years.²¹

CAP, along with influenza, is the leading cause of death due to an infectious cause in the US.²² Mortality rates are relatively low for outpatients with CAP (about 1%), but they increase substantially for patients requiring hospitalization (~15%) and those admitted to the ICU (30%-40%).²¹ Therefore, once a diagnosis of CAP is made, it is important to first determine the appropriate site of care for the patient.

SITE OF CARE DECISION

We present two typical cases to emphasize the importance of site of care.

Case 1	Case 2
 72-year-old male Fever: 100°F Respiratory rate: 22 per minute Blood pressure: 109/69 mmHg Physical findings: Rales at the right base with dullness to percussion Do you need to know anything else to make a decision about site of care? 	 68-year-old female Fever: 101°F Respiratory rate: 32 per minute Blood pressure: 109/78 mmHg Rales at right base with dullness to percussion Alert BUN level: 25 mg/dL What do you think is the appropriate site of care
	for this patient?

Discussion on these cases is presented on page 13

Whether a patient requires hospitalization depends on the following factors:

1) mortality prediction tools,

- 2) social circumstances of the patient, and
- 3) co-existing conditions.²⁰

Several mortality prediction tools have been developed to help assess the severity of illness **(Table 5)**.

• In the 1990s, Fine and colleagues developed the PORT (Pneumonia Outcomes Research Team) Severity Index (PSI) that used a combination of demographic variables, co-morbidities, physical observations, and laboratory and radiographic findings.²³ However, practical application of the PSI score in primary care can be particularly difficult given the time required and the need for laboratory findings.

- The CURB-65 criteria were developed to provide a simpler and more practical tool for PCPs to help decide whether a patient can be treated as an outpatient.²⁴ Though the CURB-65 criteria offers an improvement in the ease of use compared to the PSI score, there is still a laboratory requirement to assess uremia.
- The CRB-65 criteria, by eliminating the blood urea requirement, offer a more convenient tool to assess patient risk.²⁵

CURB-65	24		CRB-65 ²⁵	
CURB- 65 score based on assigning 1 point for each of the following:		CRB-65 score based on assigning 1 point for eac of the following:		
- Low Blo	(BUN >19 tory rate od press 0 mmHg	(>30/minute)	 <u>Confusion</u> <u>Respiratory rate (>30/minute)</u> Low <u>B</u>lood pressure (<90/<60 mmHg, either value) Age >65 years 	
CURE Sco		Risk	CRB-65 Score	Risk
0 or	·1	Low risk (Home treatment)	0	Home treatment
2		Moderate risk (Short inpatient stay or very closely supervised	1	Hospital-supervised treatment
		outpatient therapy)		

Table 5. CAP mortality prediction rules

A study that compared the mortality rates of patients using the PSI, CURB-65, and CRB-65 criteria showed a strong correlation among all three methods to evaluate risk for patient mortality.²⁵ It is important to remember that these scores should be supplemented with the physician's determination of several subjective factors (such as reliability to follow-up, support of family or friends, etc.) to decide whether an inpatient or outpatient stay is in the best interest of the patient.

ETIOLOGY OF CAP

Viral pathogens are associated with only a small proportion of CAP cases (2%-15%).²⁶ *S. pneumoniae* remains the most common bacterial cause of CAP (20%-60%), including mild, moderate, and severe cases.²⁷ Other causative bacterial pathogens include *H. influenzae* (3%-10%) and atypical pathogens (10%-20%).²⁶

Similar to AECB, more severe cases of CAP are predominantly due to Enterobacteriaceae and *P. aeruginosa*, and multidrug resistance should be considered when selecting a treatment for severe cases. The choice of initial antimicrobial therapy should, therefore, depend on the patient severity of illness, the likely pathogens, and risk of resistance and multidrug resistance. *(Risk factors for resistant infections will be discussed in greater detail in Bulletin #2.)*

TREATMENT OF CAP

In 2007, the Infectious Diseases Society of America (IDSA) and the American Thoracic Society (ATS) released updated guidelines on the management of CAP in adults.²⁸ The guidelines are a helpful resource when selecting initial empiric therapy, though antimicrobial selection should also consider patient factors and local epidemiology **(Table 6)**.

Table 6. IDSA and ATS Guidelines	for the management of CAP in adults		
Out	patients		
Previously healthy patients with no risk factors for drug-resistant <i>S. pneumoniae</i> infections	 Macrolide (azithromycin, clarithromycin, or erythromycin): strongly recommended Doxycycline can be used as an alternative (weak recommendation) 		
Patients with comorbidities (such as chronic heart, lung, liver, or renal disease; diabetes mellitus; alcoholism; malignancies; asplenia; immunosuppressing conditions or use of immunosuppressing drugs) <i>or</i> who had prior use of an antimicrobial within the past 3 months (in which case an alternative from a different class of agents should be selected) <i>or</i> other risk of a drug-resistant <i>S. pneumoniae</i> infection	 Respiratory fluoroquinolone (moxifloxacin, gemifloxacin*, or levofloxacin [750 mg]): strongly recommended or β-lactam + macrolide: strongly recommended 		
In regions with a high rate (>25%) of infection with high-level (≥16 μg/mL) macrolide-resistant <i>S. pneumoniae</i>	An alternative agent should be considered for any patient, including those without comorbidities. • Respiratory fluoroquinolone • High-dose amoxicillin • Amoxicillin-clavulanate • Ceftriaxone • Cefpodoxime • Cefuroxime • Doxycycline		
<i>Note:</i> For outpatient treatment, these recommendations should adequately cover the vast majority of CAP pathogens. ²⁸ Exceptions may be the small number of <i>P. aeruginosa</i> CAP cases as well as community-associated methicillin-resistant <i>Staphylococcus aureus</i> (CA-MRSA) infections. Clinicians should be aware of specific epidemiological patterns or clinical presentations to detect these types of infections, especially if the patient does not respond to initial therapy.			
Hospitali	zed Patients		
In the general medical ward	Respiratory fluoroquinolone: strongly recommended or B-lactam + macrolide: strongly recommended <i>Note:</i> Doxycycline can be used as an alternative to a macrolide.		
Admitted to the ICU	 β-lactam + either azithromycin or fluoroquinolone. For patients suspected of <i>Pseudomonas</i> infection, an antipneumococcal, antipseudomonal β-lactam (piperacillin- tazobactam, cefepime, imipenem, or meropenem) + either ciprofloxacin or levofloxacin (750-mg dose) 		

*Not currently marketed in the US

CASE I DISCUSSION

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RTI RESISTANCE

This patient likely has CAP and for complete and comprehensive evaluation using the CRB-65 criteria, you will need to assess the patient's mental status. (To use the CURB-65 criteria, you will additionally need to conduct a laboratory blood test to evaluate renal function [BUN]).

If the mental status and BUN levels are normal, this patient will only have a score of 1 for either criteria (age >65 years), suggesting mild illness and can likely be treated on an outpatient basis. However, before discharging the patient to home care, it is important to assess his social environment and support group (family support) as well as his reliability and accessibility for follow-up.

CASE 2 DISCUSSION

CAP is suspected and the CURB-65 criteria can be used to assign a point for age, respiratory rate, and uremia. This results in a score of 3. Her CRB-65 score is 2. This patient should, therefore, be admitted to the hospital. ICU admission should be considered depending on the presence of other comorbidities.

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PLICATION

SELF-ASSESSME Release Date: September 9, 20	ENT, EVALUATION, AND CREDI D09 Expiration Date: September 9, 2010		PLICAI Serial #: CV	
Select your professional title: Phy				
, , ,	ching hospital Community hospital LTAC Other			
	improve the quality of future continuing education activities. Please answer			ons and
SELF-ASSESSMENT (Please check the most	LEARNING OBJECTIVES: Was the learning objective met? 1. Determine when an antimicrobial agent is needed to treat a	Yes	Somewhat	No
appropriate answers) What percent of acute bronchitis episodes are caused by viral infections?	respiratory tract infection (RTI) If you answered 'No', please explain why			
□ 25% □ 50% □ 75% □ >90%	SCIENTIFIC CONTENT: Please rate Excellent 1. The scientific content of this activity was Image: Content of the scientific was 2. The level of expertise of the authors was Image: Content of the scientific was	Good	Fair	Poor
Which of the following is not a cardinal symptom of an AECB episode? Fever Increased sputum volume Increased sputum purulence Increased dyspnea	 2. The level of expertise of the authors was OVERALL EVALUATION 1. This activity met my expectations. 2. The content was relevant to my practice. 3. This activity was fair and balanced? 4. This activity was without commercial bias. If you answered 'No' to 3 or 4 please explain. 	Yes	Somewhat	
The most common bacterial cause of community-acquired pneumonia is:	LEARNING FORMAT	Yes	Somewhat	No
☐ Haemophilus influenzae ☐ Streptococcus pneumoniae ☐ Staphylococcus aureus	 The format enhanced achievement of learning objectives. The format was easy to follow and understand. 			
Moraxella catarrhalis	PRACTICE APPLICATION			
Which of the following is not part of the CURB-65 criteria to evaluate severity of illness in CAP patients?	1. What aspects of this activity were most relevant to your practi	ce?		
Respiratory rate Low blood pressure Cough Uremia	2. Will you make changes to your practice setting based on parti Why or why not?	cipation in	this activity?	
According to the 2007 IDSA/ ATS guidelines, which agent is recommended for outpatient treatment of CAP in a previously healthy patient with no recent	3. What aspects of RTI do you need to learn more about in ord performance? DO YOU HAVE (1) ANY SUCCESSIONS FOR IMPROVING	-		ce
history of antimicrobial use? Penicillin Macrolide Fluoroquinolone Cephalosporin	DO YOU HAVE (1) ANY SUGGESTIONS FOR IMPROVIN (2) ANY ADDITIONAL COMMENTS?	IG 1 1115 A	C11411 X OF	

CREDIT APPLICATION (Please Print Clearly) Name and Degree					
Address	Cit	У	State ZI	[P	
Email			May we contact you by e-mail?	Yes No	
Type of Credit requested	\square MD/DO AMA PRA Category 1 Credit TM	Other			
I certify that I have reviewed in its entirety RTI Resistance On the Frontline of Care: PCPs Fight Back! Bulletin 1: To Prescribe or Not:					
Differentiating the Need for	Antimicrobials in RTIs. Signature		Date		