RTI RESISTANCE

BULLETIN 3

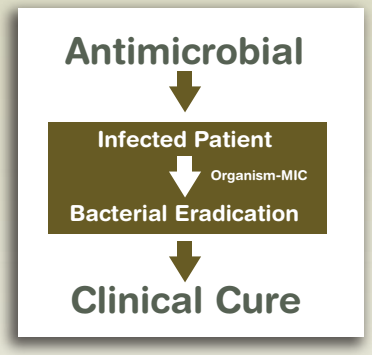
HOW TO OPTIMIZE PATIENT OUTCOMES AND MINIMIZE RESISTANCE DEVELOPMENT

FROM THE EDITORS' DESK

The previous two e-Bulletins of this series discussed two important aspects when diagnosing and managing community-acquired respiratory tract infections (RTIs):

1. differentiating between a viral and bacterial infection to guide when an antimicrobial is appropriate
2. recognizing the threat of antimicrobial resistance and identifying patients with risk factors for resistant infections.

Figure 1. Schematic Illustrating Ideal Antimicrobial Treatment of Infection



A thorough understanding of these aspects can be critical when selecting an appropriate antimicrobial agent with the goals of optimizing clinical outcomes while also minimizing the risk of resistance development. To achieve these goals, it is also important to have an understanding of how antimicrobials work in the body to eradicate an infection. As shown in **Figure 1**, the path to success begins with the administration of an antimicrobial to the infected patient. Ideally, this leads to eradication of the offending bacteria and clinical cure. However, when clinical success is not achieved, it can be difficult to understand what has occurred that led to failure. Information related to the pathogen and the drug can be helpful in predicting the clinical outcome. To do this, we need to know the susceptibility of the pathogen to the antimicrobial (minimum inhibitory concentration (MIC)) and the pharmacokinetic (PK) and pharmacodynamic (PD) properties of the antimicrobial agent used to treat the infection.

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IN THIS BULLETIN

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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 multicomponent initiative 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
- Optimize antimicrobial therapy to achieve successful outcomes

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OPTIMAL USE OF ANTIMICROBIALS FOR RTIs

The goal of antimicrobial therapy is to provide an effective drug in sufficient concentration and for a sufficient amount of time to kill all causative pathogens and achieve clinical cure.[1] Though several classes of antimicrobials are commonly used and recommended for the treatment of community-acquired RTIs, evidence is beginning to suggest that using more potent agents (or higher doses) can provide both clinical and economic benefits. For example, several studies with the fluoroquinolones have shown these agents achieve rapid eradication of respiratory tract pathogens and may be associated with earlier resolution of symptoms when compared to other classes of agents for the treatment of ABECB or CAP.[2-4]

More rapid eradication of the pathogen and earlier resolution of symptoms can have several benefits for both the patient and physician, but also for the environment at large.

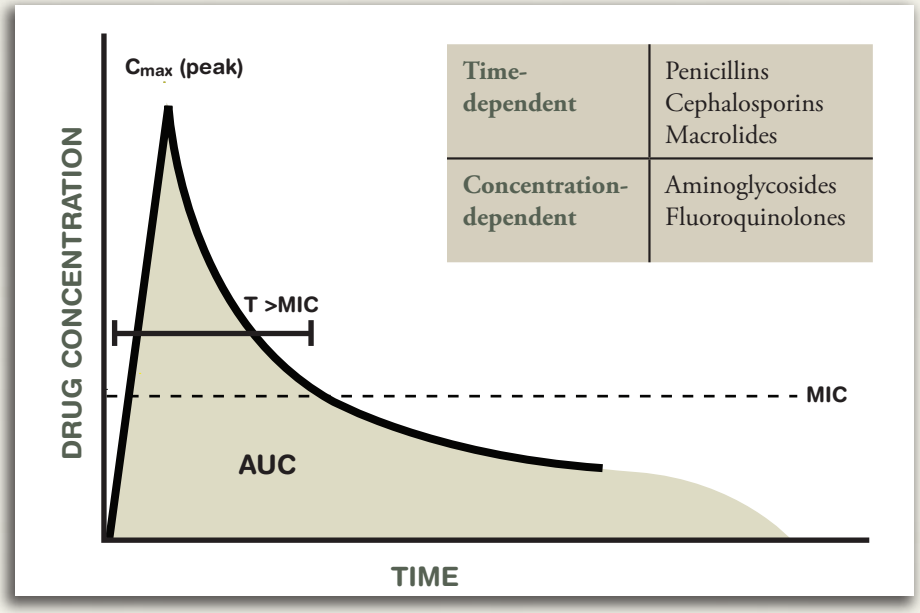
- Rapid and complete eradication of the causative pathogen minimizes the risk of resistance development.
- Patient satisfaction is achieved when effectively treated and can return to normal activities as early as possible.[5] More rapid killing translates into fewer bacteria at the site of infection and earlier symptom resolution.
- Rapid eradication can lead to shorter courses of therapy, which decreases the risk of the emergence of selected resistant organisms.[6]
- Patients who begin to respond after a few days of therapy will be less likely to call physicians for a subsequent office visit or request another antimicrobial regimen. This saves the physician time and resources to see other patients and reduces unnecessary antimicrobial prescriptions, thus reducing overall antimicrobial usage.
- A more potent agent (that is, exhibits greater in vitro activity) is less likely to result in treatment failure that could potentially require hospitalization and substantially increase overall healthcare costs.[4]

PHARMACOKINETICS AND PHARMACODYNAMICS OF ANTIMICROBIALS: A PRIMER

Dosing regimens are designed to attain PK/PD targets that increase the probability of achieving **clinical efficacy** and **preventing the emergence of resistance.**

Antimicrobial agents can be grouped into those that exhibit concentration-dependent bacterial killing and those that exhibit time-dependent bacterial killing **(Figure 2)**. The characteristics of the drug dictate the required PK/PD targets that will lead to eradication of infection.[7, 8]

Figure 2. Pharmacokinetic/Pharmacodynamic Parameters of Antimicrobials



Time-dependent Agents

For time-dependent agents, the PK/PD target relates to the proportion of time the drug concentration remains above the MIC during a dosing interval (T>MIC).[8, 9] The optimal T>MIC can vary depending on the class of antimicrobial agent-it is estimated to be 50% for penicillins and 60%-70% for the cephalosporins.[10]

Several dosing strategies can be used to maximize the T>MIC of time-dependent agents. Shortening the dosing interval *(increasing the frequency of dosing without increasing the total daily dosage)* may increase the T>MIC.[10] However, using higher doses may not have a corresponding impact on T>MIC *(doubling the dose will not necessarily double the T>MIC)*. If susceptibility results are available for the infecting organism, optimized dosing strategies may also involve using an agent with greater in vitro potency *(a lower MIC)* for that particular pathogen to increase the T>MIC.

Concentration-dependent Agents

For concentration-dependent agents, successful outcomes are associated with meeting targets related to:

- the peak concentration to MIC ratio (C_{max}/MIC)
- the area under the concentration-time curve to MIC ratio (AUC/MIC).[9]

For these agents, maximizing exposure with higher doses or with consolidated dosing (that is, the same total drug amount in less frequent doses) can be important strategies to achieve optimal PK/PD targets.

Table 1. Optimal PK/PD Targets for Concentration-dependent Agents[11]

For optimal antimicrobial effect	C_{max}/MIC >8-10 AUC/MIC >100-125
To minimize resistance development	AUC/MIC >100
Values are applicable for both gram-positive and gram-negative bacteria	

Higher doses of fluoroquinolones increase the probability of meeting AUC/MIC targets. For *S. pneumoniae* infections, an AUC/MIC ratio of 30-35 is generally recommended for successful clinical outcomes.[9] PK/PD studies in humans indicate that this ratio may actually need to be at least 100 to 125 for optimal antimicrobial effect. Some research suggests that even higher AUC/MIC ratios are needed for maximal bactericidal killing with the fluoroquinolones.[11, 12]

Table 2. The Benefits of a Higher AUC/MIC Target[11]

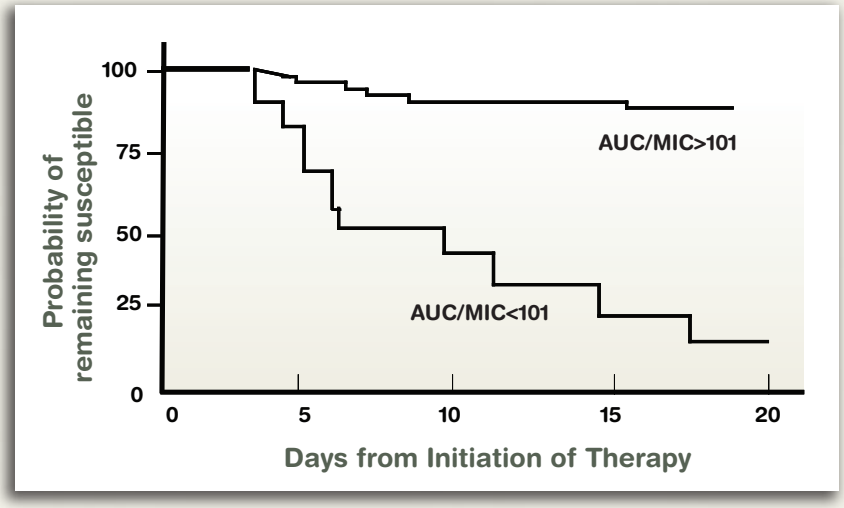
AUC/MIC = 30-50	AUC/MIC >250
• Little to no killing in 7 days • Inoculum reduction, with reliance on host defense • Selection of resistant sub-populations, capable of surviving unless host defense can remove them • Colonization of site with residual organisms	• One day killing of *S. pneumoniae* (in vitro ~1 hr killing) • Killing of one-step mutants, though probably slower • Faster relief of signs and symptoms of infection • Shorter courses of therapy are possible since therapy can be terminated 4-5 days after killing

The probability of achieving optimal PK/PD targets by the fluoroquinolones can vary by agent and dosing regimen. The 750-mg dose of levofloxacin nearly doubles the AUC compared to the 500-mg dose and increases the probability of meeting an AUC/MIC target of 35, which is particularly important for isolates with higher MIC values.[13, 14]

THE IMPORTANCE OF ATTAINING PK/PD TARGETS TO MINIMIZE RESISTANCE DEVELOPMENT

The ability to attain PK/PD targets can be an important risk indicator for resistance development. One study compared AUC/MIC ratios to the probability of the pathogen remaining susceptible over the course of treatment in 107 patients with nosocomial lower RTIs **(Figure 3)**.[15] In patients where therapy achieved an AUC/MIC >100, resistance occurred in 9.2% of the patients. However, if the AUC/MIC failed to reach 100, resistance began to occur at Day 4 and eventually 82.4% of cases developed resistance to the antimicrobial.

Figure 3. Relationship Between AUC/MIC and Probability of Resistance Development[15]



The emergence of resistant isolates can have important implications in the community setting. If an ineffective agent or dose is chosen to treat a RTI, the data above suggests that continuing therapy for a longer duration will not benefit the patient as this practice will only increase the risk of resistance development through selection pressure.

Therefore, it is important to select the appropriate agent and dose to eradicate the infection as quickly as possible.

OPTIMIZING THE USE OF FLUOROQUINOLONES FOR *S. PNEUMONIAE* INFECTIONS

Over the past 15 years, the fluoroquinolones have been the most studied class of antimicrobials to evaluate the relationship between attaining PK/PD targets and clinical outcomes. PK/PD studies have often been done to determine dosing regimens in order to ensure maximum killing potential. One example of this was the adoption of the high-dose, short-course levofloxacin regimen.[6]
In a prospective, randomized, double-blind clinical trial, the 750-mg, 5-day levofloxacin course was compared with the traditional course of 500 mg of levofloxacin for 10 days for the treatment of community-acquired pneumonia (CAP).[16] Both regimens achieved comparable clinical and microbiological outcomes but a significantly greater percentage of patients receiving the high-dose regimen had more rapid resolution of symptoms, including fever.[17]

Among the fluoroquinolones, moxifloxacin has the highest probability to attain the PK/PD target required to prevent development of resistance (AUC/MIC >100) when treating *S. pneumoniae* infections.[18] However, does this ability to attain PK/PD targets impact clinical outcomes?
To demonstrate this, moxifloxacin was compared to levofloxacin (500 mg) in a prospective, randomized, double-blind trial for the treatment of hospitalized patients (≥65 years) with CAP.[19]
At the test-of-cure visit (5-21 days after completion of therapy), there was no significant difference in the clinical cure rate between those treated with moxifloxacin (92.9%) and levofloxacin (87.9%; P=.2), even when patients were stratified by disease severity or age. However, at the on-treatment visit (3 to 5 days after the start of therapy), a significantly greater percentage of patients receiving moxifloxacin had achieved clinical recovery than those receiving levofloxacin (97.9% versus 90.0%; P=.01). Clinical recovery was defined as absence of acute signs and symptoms related to the infection or reduction in severity and/or number of signs and symptoms of infection.

These studies suggest that using a more potent agent or optimized dosing regimens can lead to more rapid resolution of CAP symptoms. This may be attributed to a greater probability of attaining PK/PD targets associated with clinical success, rapid eradication, and prevention of resistance development.

PK/PD RELEVANCE IN PRIMARY CARE:
THE EXAMPLE OF COPD PATIENTS

The importance of understanding AUC/MIC values in primary care has been recently demonstrated in patients with chronic obstructive pulmonary disease (COPD). RTIs in COPD patients can progress to either an acute exacerbation of chronic bronchitis (AECB) or a more serious case of CAP. However little is known as to what factors increase the risk of progression to CAP in these patients.

CLINICAL CONSEQUENCES OF FAILING TO ATTAIN PK/PD TARGETS

A study by File and colleagues evaluated the severity of underlying pulmonary disease and the impact of antimicrobial choice on progression to CAP.[20] Nine databases that included 5126 COPD patients were included in the study. Of these patients, 811 developed AECB and 343 developed CAP. The bacterial etiology of these infections is shown in **Table 3**.

Table 3. Etiology Among COPD Patients with AECB or CAP[20]

Pathogen	AECB (n=811)	CAP (n=343)
S. pneumoniae	4%	13%[a]
H. influenzae	7%	4%[b]
Other bacteria	21%	4%[a]
No growth	2%	36%[a]
No culture	66%	43%[a]

[a]$P<.001$ [b]$P<.05$

Patients with *S. pneumoniae* infection were more likely to progress to CAP, and a key determinant for this progression was the AUC/MIC. A total of 212 cases of *S. pneumoniae* infection were included in the analysis, and 113 (53%) were treated with an antimicrobial (**Table 4**).[20] When an AUC/MIC ≥100 was achieved, only 34.9% of the patients progressed to CAP. However, when AUC/MIC was below 100, nearly 92% of patients progressed to CAP ($P<.001$). This higher progression rate to CAP was maintained regardless of COPD severity.

Interestingly, all patients with a *S. pneumoniae* infection who were not treated with an antimicrobial were eventually hospitalized, demonstrating the importance of using an antimicrobial for COPD patients with *S. pneumoniae* infections. These observations suggest that COPD patients who develop AECB caused by *S. pneumoniae* can have suboptimal outcomes, such as progression to CAP, if treated with suboptimal antimicrobial therapy.

Table 4. Antimicrobial Use and AUC/MIC≥100 in COPD Patients with *S. pneumoniae* CAP[20]

Antimicrobial	% Patients Receiving an Antimicrobial (n=113)	% Patients Attained AUC/MIC≥100 (n=43)	% Patients Attained AUC/MIC<100 (n=70)
Macrolide	55.3	18.6	71.4
Fluoroquinolone	27.0	53.5	15.3
Cephalosporin	10.6	7.0	12.2
Penicillin	7.1	20.9	1.1
Multiple drugs	24.8	0	40.0

ECONOMIC CONSEQUENCES OF INEFFECTIVE TREATMENT

In addition to clinical consequences of COPD progression to CAP, there is also a substantial economic consequence. A sub-analysis of COPD patients with a lower RTI infected with *S. pneumoniae* found:

- The mean cost of treatment for these patients was $3050.[21]
- If patients were not prescribed an antimicrobial, the mean cost increased to $8768.
- For patients who received an antimicrobial but failed to achieve an AUC/MIC of 100, the mean cost was $5529.
- The lowest overall cost of $1117 was for patients who achieved PK/PD targets.

The higher costs were likely attributed to greater frequency of clinical failure and hospitalization of these patients.

Studies have evaluated the increased cost due to treatment failure of RTIs attributed to antimicrobial resistance. A multicenter, retrospective, observational study involved 122 patients with *S. pneumoniae* CAP who required hospitalization after failing to respond to initial outpatient treatment with a macrolide for 2 or more days.[22] Over half of the patients were bacteremic and 71% were infected with a macrolide-resistant strain. The mean hospital length of stay was 8.7 days, including 1.3 days in a critical care unit and 1.4 days of mechanical ventilation. The mean cost of treating a patient with a macrolide-resistant infection was $5139 higher than the cost of treating a patient infected with a macrolide-susceptible strain ($14,153 vs $9,014; *P*=.011). For patients with bacteremia, the cost of treating a resistant strain was nearly double compared to treating a susceptible strain ($16,563 vs $8,537; *P*=.004). As previously discussed in e-Bulletin Issue 2, several studies have associated antimicrobial resistance with clinical failures, particularly with the macrolides.[23-25]

It is important to keep in mind that reducing overall healthcare costs does not necessarily mean selecting the least expensive drug. A pharmacoeconomic review evaluated the costs of treating CAP, acute bacterial sinusitis and AECB with a fluoroquinolone versus other, less expensive antimicrobials.[26] The study found that treatment with a fluoroquinolone was more effective and resulted in lower overall healthcare costs versus other agents despite the higher initial drug costs.

RELEVANCE ALERT!

How to Adopt this New Model in the Practice Setting

The use of AUC/MIC values can be extremely valuable when treating patients with RTIs. However, it is impractical to expect primary care physicians to conduct all the necessary laboratory tests needed to derive this value as well as delay treatment until culture results are available for each patient with an RTI. Therefore, there are some important steps a physician can take to increase the probability of achieving an effective AUC/MIC.

1. Know your local epidemiology, in particular, the resistance rates of common RTI pathogens

Penicillin non-susceptibility by *S. pneumoniae* in the United States is approximately 35% while macrolide resistance approaches 30%.[27-29] These rates can vary greatly based on geographic regions. Fluoroquinolone resistance remains below 2% for levofloxacin and below 1% for moxifloxacin.

2. Choose the appropriate drug and dose to optimize AUC/MIC

If using a fluoroquinolone, this may mean to use the highest approved dose (such as the 750-mg dose of levofloxacin) or use an agent with greater in vitro activity against the pathogen (moxifloxacin). This will help to ensure rapid eradication of the pathogen and minimize the risk of resistance emergence.

3. Factors to consider

1. Does the patient have a *S. pneumoniae* infection?
   The frequency of *S. pneumoniae* can range from 5% to 45%, depending on underlying comorbidities. Approximately 15% of RTI episodes in COPD patients are attributed to this pathogen. Culturing sputum samples from each of these patients would impose a time and cost burden. It will be important to recognize a few signs that may indicate a bacterial infection requiring antimicrobial treatment versus a viral infection. These signs include fever, respiratory difficulty, and a rapid change in condition over the past 24 hours.
2. When the patient has a *S. pneumoniae* infection, selecting an effective antimicrobial at the correct dose is critical (the goal of an AUC/MIC >100).
3. Failure is expensive.
   Most failures of *S. pneumoniae* infections can be explained by an AUC/MIC <100.
4. Rapid eradication is better than slower eradication when all other factors are equal.

TIPS FOR THE 10-MINUTE OFFICE VISIT AND EVALUATION

In the high-paced nature of primary care medicine, physicians often have less than 10 minutes to assess and treat a patient with a suspected RTI. This short window of time must be used efficiently to properly evaluate the patient and avoid further deterioration while also minimizing the inappropriate use of antimicrobials. Important criteria to evaluate in each case include:

- Evaluate current and past medical history
- Determine the severity of presenting respiratory illness for sinusitis, bronchitis, or pneumonia
- Is the infection viral or bacterial?
  – If bacterial, which is the likely organism?
- Is there likely bacterial resistance from recent prior antimicrobial exposure?
- Should an antimicrobial be given for this infection?
- Are there any adverse effect risk factors? Drug-drug interactions?
- Which antimicrobial, which dose, and what duration of therapy?

In conclusion, to appropriately manage RTIs in the community setting, there are a number of considerations that a physician must keep in mind prior to prescribing an antimicrobial. One of these considerations is to remember that the most common reasons for primary care office visits are due to suspected or proven infections – the vast majority of these are caused by viruses. Guidelines are available to help identify patients with a viral infection who should not be given an antibiotic.

On page 12 of this e-Bulletin is a list of ***"Clinical Pearls for the Management of RTIs."*** It can be printed and used as a convenient guide when evaluating a patient with a RTI to determine when an antimicrobial is appropriate, how to select the antimicrobial, and how to optimize the dose and duration for clinical effectiveness and to prevent the emergence of resistance.

CLINICAL PEARLS FOR THE MANAGEMENT OF RTIs

1. Decide whether signs and symptoms are likely of viral or bacterial origin

2. If a viral infection is suspected, do not prescribe an antimicrobial
- a. Educate the patient on the consequences of overusing antimicrobials
- b. Suggest alternative approaches to alleviate symptoms

3. Utilize diagnostic approaches to confirm a bacterial infection and severity of illness

4. Determine appropriate site of care using risk assessment tools (e.g., CURB-65)

5. Patient factors to consider:
- a. Presence of risk factors for a resistant infection
- b. Recent prior antimicrobial use (if so, prescribe a different class of agent)

6. Environmental factors to consider:
- a. Local resistance trends of common respiratory tract pathogens
- b. Occurrence of a local outbreak

7. Consider antimicrobials that are highly active against the suspected pathogen

8. Prescribe an appropriate dose and duration of therapy to:
- a. Eradicate the infection
- b. Minimize the risk of resistance development

9. Emphasize to the patient the importance of:
- a. Initiating therapy as soon as possible (if a first dose is not given at the office visit)
- b. Following the prescription order instructions
- c. Using precautions to minimize exposure to others (i.e., stay home from work, school, etc.)

10. For patients who have failed initial therapy:
- a. Consider the reason for failure (i.e., drug, dose, duration, route of administration, etc.)
- b. Re-assess site of care
- c. Consider additional microbiologic tests (culture and susceptibility test)

VIEWPOINT

DEAD BUGS DON'T MUTATE!

Considerations to Prevent the Emergence of Antimicrobial-Resistant Strains

There are a number of tactics that primary care physicians can use to minimize the risk of antimicrobial resistance development when treating patients with bacterial RTIs:

- Consider shorter duration of therapy (5-7 days), particularly when using optimized dosing regimens
- Choose agents that are more likely to attain PK/PD targets needed for effective treatment (e.g., AUC/MIC ≥100)
- Educate your patients on the importance of adherence to therapy to ensure the full prescribed regimen is used and treatment is not terminated before complete eradication occurs

The use of optimized dosing regimens has the potential to eradicate the infection more rapidly. This can have important benefits to both the patient and the primary care physician, including:

- A reduced risk of resistance development and spread of resistant strains to the community
- A decreased risk of treatment failure leading to hospitalization
- More rapid resolution of symptoms
- Reduced follow-up phone calls and office visits from patients with persistent symptoms

Rapid eradication of *Streptococcus pneumoniae* is better than slower eradication, all other factors being equal, especially because **dead bugs don't mutate.**

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SELF-ASSESSMENT, EVALUATION, AND CREDIT APPLICATION

Release Date: December 19, 2009 Expiration Date: December 19, 2010 Center Serial #: CV3113-3

Select your professional title: ☐ Physician ☐ Physician Assistant ☐ Other _____

Your evaluation and suggestions will help improve the quality of future continuing education activities. Please answer the following general questions and provide written comments. Thank you for your cooperation.

SELF-ASSESSMENT
(Please check the most appropriate answers)

Which class of antimicrobial agents exhibits concentration-dependent activity?

- ☐ Penicillins
- ☐ Cephalosporins
- ☐ Fluoroquinolones
- ☐ Macrolides

For the fluoroquinolones, the PK/PD target required to minimize resistance development is:

- ☐ T>MIC of 30%
- ☐ T>MIC of 50%
- ☐ AUC > 250
- ☐ AUC/MIC ≥100

What percent of COPD patients with *S. pneumoniae* infection and who were not given an antibiotic required hospitalization?

- ☐ 0%
- ☐ 33%
- ☐ 75%
- ☐ 100%

What percent of COPD patients with *S. pneumoniae* infection and who failed to achieve an AUC/MIC≥100 progressed to CAP?

- ☐ 40%
- ☐ 60%
- ☐ 80%
- ☐ >90%

What PK/PD target is required for an optimal effect for the cephalosporins?

- ☐ Cmax >8
- ☐ AUC/MIC>50
- ☐ T>MIC of 50%
- ☐ T>MIC of 60%

LEARNING OBJECTIVES: Was the learning objective met?

	Yes	Somewhat	No
1. Optimize antimicrobial therapy to achieve successful outcomes	☐	☐	☐

If you answered 'No', please explain why

SCIENTIFIC CONTENT: Please rate

	Excellent	Good	Fair	Poor
1. The scientific content of this activity was	☐	☐	☐	☐
2. The level of expertise of the authors was	☐	☐	☐	☐

OVERALL EVALUATION

	Yes	Somewhat	No
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.

LEARNING FORMAT

	Yes	Somewhat	No
1. The format enhanced achievement of learning objectives.	☐	☐	☐
2. The format was easy to follow and understand.	☐	☐	☐

PRACTICE APPLICATION

1. What aspects of this activity were most relevant to your practice?

2. Will you make changes in your practice based on participation in this activity? Why or why not?

3. What aspects of RTI do you need to learn more about in order to improve your practice performance?

DO YOU HAVE (1) ANY SUGGESTIONS FOR IMPROVING THIS ACTIVITY or (2) ANY ADDITIONAL COMMENTS?

CREDIT APPLICATION (Please Print Clearly) Name and Degree _____

Address _____ City _____ State _____ ZIP _____

Email _____ May we contact you by e-mail? ☐ Yes ☐ No

Type of Credit requested ☐ MD/DO *AMA PRA Category 1 Credit™* ☐ Other _____

I certify that I have reviewed in its entirety *RTI Resistance On the Frontline of Care: PCPs Fight Back!* Bulletin 3: *How to Optimize Patient Outcomes and Minimize Resistance Development* Signature _____ Date _____