Applying Antimicrobial Stewardship Principles to the Treatment of CABP and ABSSSI

COMPLYING WITH CMS CRITERIA AND CLINICAL GUIDELINES

Ask the Experts: Strategies for Optimizing Antimicrobial Use in Community-Acquired Bacterial Pneumonia

ASHP Advantage is coordinating a series of learning opportunities to provide pharmacists with strategies for managing the treatment of community-acquired bacterial pneumonia (CABP) and acute bacterial skin and skin structure infections (ABSSSI). These opportunities are designed to build on each other to provide an evidence-based approach to managing the treatment of patients with CABP and ABSSSI in accordance with Centers for Medicare & Medicaid Services (CMS) requirements and clinical guidelines from authoritative sources.

A live symposium was conducted on December 9, 2013, during the 48th ASHP Midyear Clinical Meeting and Exhibition in Orlando, Florida. The symposium was simultaneously broadcast, enabling a total of more than 950 individuals to participate. Attendees submitted questions about unresolved issues related to the treatment of CABP and ABSSSI, and these questions served as a guide for Initiative Chair John Esterly, Pharm.D., BCPS (AQ-ID), when he developed content for a live webinar held on March 25, 2014. This webinar and emerging literature are the primary sources of content explored in the two e-newsletters that are part of the educational initiative.

If you missed the Midyear symposium, it is available as a web-based activity and is approved for 2 hours of continuing pharmacy education. Its on-demand format is convenient since it may be completed at any time. For more information and to access the web-based activity, go to the initiative web portal at www.ashpadvantage.com/id.

Visit the CABP/ABSSSI web portal to listen to Dr. Esterly and fellow faculty Drs. Scott Bergman and Neil A. Davis discuss important issues related to the topic. The discussion is available in three parts, each lasting approximately12 minutes:

- Considerations for incorporating new ABSSSI and CABP treatment options into clinical practice
- Controversies and conundrums in the treatment of CABP
- The role of the pharmacist in ABSSSI and CABP—taking action

Sign up to be notified of updates related to this educational initiative. The second e-newsletter in this series will cover questions addressed in the Ask the Experts webinar associated with ABSSSI.
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Why focus on CABP?

The clinical and economic consequences of CABP are substantial in the United States. Pneumonia is among the leading causes of death in the United States, accounting for more than 60,000 deaths each year.[1] An estimated 5-6 million cases of CABP occur each year in the United States, resulting in 4.2 million ambulatory care visits and 1.2 million hospitalizations. Admission to an intensive care unit (ICU) is required in 10% to 20% of patients hospitalized with CABP, with a mean length of stay of at least 5 days. One in five patients hospitalized with CABP is readmitted within 30 days after discharge. The annual cost of CABP exceeds $17 billion in the United States. The annual cost is expected to increase by $2.5 billion by 2040 because infections are most common in the elderly, and the U.S. population is aging.[2]

This e-newsletter features frequently asked questions (FAQs) addressed by the faculty pertaining to CABP. Answers to FAQs about ABSSSI will be provided in the next e-newsletter.

Q What is the primary basis used by CMS for evaluating hospital care provided to patients with CABP?

A The agency is most interested in its national hospital inpatient quality measures for pneumonia: (1) blood cultures performed within 24 hours prior to or 24 hours after hospital arrival for patients who were transferred or admitted to the ICU within 24 hours of hospital arrival (PN-3a) and (2) initial (i.e., empiric) antibiotic selection for community-acquired pneumonia (CAP) in immunocompetent patients (PN-6), immunocompetent ICU patients (PN-6a), and immunocompetent non-ICU patients (PN-6b).[3] Initiating antibiotic therapy within 6 hours after arrival at the hospital (PN-5c) is no longer required by CMS. The agency expects to see blood cultures for all ICU patients and guideline-concordant antibiotic therapy for non-ICU and ICU patients (Table 1). Exceptions to CMS requirements for initial antibiotic therapy are allowed for patients with or at risk for healthcare-associated pneumonia (e.g., hospitalization or residence in a nursing home or extended care facility within the last 90 days, chronic dialysis, wound care, tracheostomy care, or ventilator care provided by a health care professional within the last 30 days).[3]

Risk-adjusted mortality and 30-day hospital readmission rates also are of interest to CMS. Reimbursement by CMS will be reduced if risk-adjusted 30-day readmission rates are higher than expected.

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Q How can antimicrobial stewardship program activities in hospitals be coordinated with efforts to meet CMS requirements for treating patients with CABP?

A Institutional policies, protocols, and standardized order sets can be established to ensure appropriate empiric treatment of CABP in accordance with CMS quality measures and evidence-based treatment guidelines from authoritative groups, such as the American Thoracic Society and Infectious Diseases Society of America.[3,4] Policies and protocols should be designed to avoid the excessive and inappropriate use of antibiotics associated with the emergence of antimicrobial resistance. The CMS allows exceptions to its requirements for initial antibiotic therapy for various scenarios (e.g., patients transferred from another acute care facility). Criteria for the use of antipseudomonal therapy in CABP patients and differentiating between healthcare-associated pneumonia,

Table 1. CMS Quality Measures for Initial Antibiotic Treatment for CAP[3,4,a]

Non-ICU patients (one of the following four options)	**Non-ICU patients at risk for infection with *Pseudomonas* species[b]** (one of the following three options)	**ICU patients** (one of the following four options)
β-lactam + macrolide	Antipseudomonal β-lactam + antipseudomonal quinolone	β-lactam + macrolide
Antipneumococcal quinolone	Antipseudomonal β-lactam + aminoglycoside + quinolone	β-lactam + quinolone
β-lactam + doxycycline	Antipseudomonal β-lactam + aminoglycoside + macrolide	β-lactam + aminoglycoside + macrolide
Tigecycline		β-lactam + aminoglycoside + quinolone

CAP = community-acquired pneumonia; CMS = Centers for Medicare & Medicaid Services; ICU = intensive care unit

aBased on a consensus of opinion of representatives from the Centers for Disease Control and Prevention, Infectious Diseases Society of America, Canadian Infectious Disease Society, Canadian Thoracic Society, and American Thoracic Society.

bRisk factors for infection with *Pseudomonas* species include advanced chronic obstructive pulmonary disease treated with corticosteroids, structural lung disease (e.g., bronchiectasis), and frequent antibiotic use.

which is commonly associated with *Pseudomonas aeruginosa*, should be established. Standardized order sets can be helpful in ensuring that the antibiotic agent, dose, route of administration, and duration of therapy are appropriate. These order sets should be incorporated into computerized prescriber order entry systems.

Q At my institution, the macrolide antibiotic azithromycin often is used in combination with a β-lactam antibiotic as empiric treatment to provide antimicrobial coverage for atypical pathogens in patients with CABP. For how long should azithromycin therapy be continued in the absence of microbiologic test results confirming the presence of atypical pathogens?

A Azithromycin is active against atypical pathogens associated with CABP, including *Mycoplasma pneumoniae*, *Chlamydophila pneumoniae*, and *Legionella* species.[5] In an analysis of 28 studies, no survival advantage or clinical benefit was associated with the empiric use of antibiotic regimens providing atypical coverage instead of regimens providing coverage for typical pathogens in hospitalized patients with CAP that was not severe.[6] In a study of 5240 adults hospitalized with CAP, a reduction in the 30-day inpatient mortality rate was associated with the use of combination therapy with a β-lactam antibiotic plus a macrolide antibiotic to provide atypical coverage instead of a β-lactam alone in patients with moderate or severe CAP (adjusted odds ratio 0.54 and 0.76, respectively), but not in those with mild CAP.[7] In another study of 529 ICU patients with severe CAP, including 270 patients with CAP and shock, the 28-day ICU mortality rate was similar with combination antibiotic therapy and monotherapy in patients without shock. However, in patients with CAP and shock, the 28-day ICU survival rate was significantly higher with combination therapy than monotherapy (hazard ratio 1.69, p=0.01).[8] Macrolide antibiotic therapy may have an immunomodulatory effect (i.e., it may modulate the host inflammatory response) in addition to its antimicrobial effects.[9] The comparative efficacy of β-lactam monotherapy, combination therapy with a β-lactam antibiotic and a macrolide antibiotic, and quinolone monotherapy for the empiric treatment of CABP is unknown.

Because the addition of azithromycin to provide atypical coverage has not been shown to be beneficial except in critically ill patients with CAP, azithromycin should not be continued indefinitely in non-critically ill patients with CAP in the absence of laboratory confirmation of the presence of atypical pathogens. Improvement in and stabilization of patient clinical status are key factors in deciding when to discontinue azithromycin in non-critically ill patients with CAP.

Q What is the role of de-escalation of antibiotic therapy in patients with CABP?

A Antibiotic de-escalation strategies to narrow the spectrum of antimicrobial activity on the basis of culture and susceptibility test results, shorten the duration of therapy, or both in adults with CAP can reduce adverse effects, antibiotic resistance, and health

care costs.[4] The diagnosis of CAP should be confirmed based on the results of radiologic examinations, culture data, and other laboratory tests (e.g., procalcitonin and C-reactive protein, which are markers of infection and inflammation, respectively). Antibiotic monotherapy should be used whenever possible based on the results of laboratory tests used to identify the pathogen and determine its antimicrobial susceptibilities. Patients with CAP should be switched from parenteral antibiotic therapy to oral therapy as soon as they are clinically stable and able to take medications orally.[10] This switch may facilitate hospital discharge if the patient has no other medical problems that require hospitalization and he or she has a safe environment/destination for transition to the outpatient setting.

Antibiotic therapy should be continued for at least 5 days in patients with CAP.[4] A longer duration of therapy may be required if initial therapy was not active against the causative pathogen or CABP was complicated by extrapulmonary infection (e.g., endocarditis, meningitis).[4] The patient should be afebrile for 48-72 hours and have no more than one CAP-associated sign of clinical instability before discontinuing antibiotic therapy. Signs of instability include temperature higher than 37.8°C (100°F), heart rate greater than 100 beats/min, respiratory rate greater than 24 breaths/min, systolic blood pressure less than 90 mm Hg, and arterial oxygen saturation less than 90% or oxygen partial pressure less than 60 mm Hg on room air.[4]

Antimicrobial stewardship programs can play an important role in de-escalating antibiotic therapy and facilitating parenteral-to-oral therapy conversion and hospital discharge in patients with CABP. Education and prospective feedback to prescribers about antibiotic selection and duration of therapy as part of antimicrobial stewardship programs have been shown to shorten the duration of antibiotic therapy and length of hospital stay in patients with CAP.[11]

Q What is the role of antimicrobial agents recently approved by the Food and Drug Administration (FDA) for the treatment of CABP and other infections? How should they be positioned on institutional formularies?

A In evaluating recently-approved antimicrobial agents for formulary addition, clinical efficacy and safety data in comparison with other evidence-based treatment options should be evaluated. Comparative cost data should be taken into consideration. The cost of administering and monitoring drug therapy and managing adverse effects as well as the drug acquisition cost should be included in cost analyses.

Ceftaroline is a new cephalosporin approved by FDA in 2010 for the treatment of CABP and ABSSSI caused by certain susceptible pathogens.[12] These pathogens include:

- *Streptococcus pneumoniae* (*S. pneumoniae*, for CABP only),
- *Staphylococcus aureus* (methicillin-susceptible strains only for CABP, and both methicillin-susceptible and methicillin-resistant strains for ABSSSI),
- *Haemophilus influenza*,
- *Escherichia coli*,
- *Klebsiella oxytoca*,
- *Klebsiella pneumoniae*,
- *Streptococcus pyogenes* (ABSSSI only), and
- *Streptococcus agalactiae* (ABSSSI only).

In two randomized trials of a total of 1228 hospitalized patients with CAP, ceftaroline 600 mg intravenously (i.v.) every 12 hours was judged noninferior in efficacy to ceftriaxone 1 g i.v. every 24 hours for 5-7 days.[13] A post-hoc retrospective subgroup analysis of 139 patients with *S. pneumoniae* revealed a higher cure rate with ceftaroline than ceftriaxone (85.5% and 68.6%, $p = 0.009$).[14] However, these findings need to be confirmed by additional research because the analysis was post-hoc and underpowered to detect a difference in efficacy in this population. Additionally, the number of multidrug-resistant strains of *S. pneumoniae* in the trials was inadequate to draw definitive conclusions.

In two phase 3 randomized trials, ceftaroline 600 mg i.v. every 12 hours was judged noninferior to a combination of vancomycin 1 g and aztreonam 1 g i.v. every 12 hours for 5-14 days for treating ABSSSI in a total of 797 patients.[15,16] Results of a retrospective analysis of clinical response data from day 3 in these studies suggests a higher response rate with ceftaroline (74.0%) than vancomycin plus aztreonam (66.2%).[17] However, questions have been raised about whether the "one size fits all" approach to vancomycin dosing used in these studies was optimal relative to evaluating early response. Ceftaroline does not appear in current evidence-based guidelines for the treatment of CABP or ABSSSI as its FDA approval came after the most recent iterations (2007 and 2005 respectively).

Prescribing restrictions should be considered to

avoid excessive use and ensure the proper use of new antimicrobial agents added to the formulary. Criteria for restricting use might include use for only FDA-approved indications, use only in specific patient populations or scenarios in accordance with institutional policies and protocols, and prescribing by only selected authorized personnel (e.g., infectious disease specialists, intensivists) after formal consultation. Institutional policies and protocols could require use of the agent for treatment of culture-confirmed or otherwise documented infection (i.e., not as empiric therapy) or for a certain type, anatomical location, or severity of infection.

Policies and procedures could include prior approval of restricted antimicrobials by a person familiar with approved use criteria or a mandatory review by a clinical pharmacist of all new orders for the restricted antimicrobial agent. Clinical decision support systems could also be programmed to alert pharmacists to new orders of the agent as a prompting mechanism if that type of technology is available.

References

1. File TM Jr, Marrie TJ. Burden of community-acquired pneumonia in North American adults. *Postgrad Med.* 2010; 122:130-41.
2. Wroe PC, Finkelstein JA, Ray GT et al. Aging population and future burden of pneumococcal pneumonia in the United States. *J Infect Dis.* 2012; 205:1589-92.
3. Centers for Medicare & Medicaid Services ,The Joint Commission. Specifications manual for national hospital inpatient quality measures. Version 4.3a for discharges 01/01/2014 to 09/30/2014. October 2013. http://www.qualitynet.org/dcs/ContentServer?c=Page&pagename=QnetPublic%2FPage%2FQnetTier4&cid=1228773265583 (accessed 2013 Nov 13).
4. Mandell LA, Wunderink RG, Anzueto A et al. Infectious Diseases Society of America/American Thoracic Society consensus guidelines on the management of community-acquired pneumonia in adults. *Clin Infect Dis.* 2007; 44(Suppl 2):S27-72.
5. Thibodeau KP, Viera AJ. Atypical pathogens and challenges in community-acquired pneumonia. *Am Fam Physician*. 2004; 69:1699-706. Available at: http://www.aafp.org/afp/2004/0401/p1699.html.
6. Eliakim-Raz N, Robenshtok E, Shefet D et al. Empiric antibiotic coverage of atypical pathogens for community-acquired pneumonia in hospitalized adults. *Cochrane Database Syst Rev*. 2012; 9:CD004418.
7. Rodrigo C, McKeever TM, Woodhead M et al. Single versus combination antibiotic therapy in adults hospitalised with community acquired pneumonia. *Thorax*. 2013; 68:493-5.
8. Rodriguez A, Mendia A, Sirvent JM et al. Combination antibiotic therapy improves survival in patients with community-acquired pneumonia and shock. *Crit Care Med*. 2007; 35:1493-8.
9. Sibila O, Restrepo MI, Anzueto A. What is the best antimicrobial treatment for severe community-acquired pneumonia (including the role of steroids and statins and other immunomodulatory agents). *Infect Dis Clin North Am*. 2013; 27:133-47.
10. Ramirez JA, Bordon J. Early switch from intravenous to oral antibiotics in hospitalized patients with bacteremic community-acquired *Streptococcus pneumoniae* pneumonia. *Arch Intern Med*. 2001; 161:848-50.
11. Avdic E, Cushinotto LA, Hughes AH et al. Impact of an antimicrobial stewardship intervention on shortening the duration of therapy for community-acquired pneumonia. *Clin Infect Dis*. 2012; 54:1581-7.
12. Teflaro (ceftaroline fosamil) prescribing information. St. Louis, MO: Forest Laboratories, Inc; 2013 Dec.
13. File TM Jr, Low DE, Eckburg PB et al. Integrated analysis of FOCUS 1 and FOCUS 2: randomized, doubled-blinded, multicenter phase 3 trials of the efficacy and safety of ceftaroline fosamil versus ceftriaxone in patients with community-acquired pneumonia. *Clin Infect Dis*. 2010; 51:1395-405.
14. Shorr AF, Kollef M, Eckburg PB et al. Assessment of ceftaroline fosamil in the treatment of community-acquired bacterial pneumonia due to *Streptococcus pneumoniae*: insights from two randomized trials. *Diagn Microbiol Infect Dis*. 2013; 75:298-303.
15. Corey GR, Wilcox MH, Talbot GH et al. CANVAS 1: the first phase III, randomized, double-blind study evaluating ceftaroline fosamil for the treatment of patients with complicated skin and skin structure infections. *J Antimicrob Chemother*. 2010; 65(Suppl 4):iv41-51.
16. Wilcox MH, Corey GR, Talbot GH et al. CANVAS 2: the second Phase III, randomized, double-blind study evaluating ceftaroline fosamil for the treatment of patients with complicated skin and skin structure infections. *J Antimicrob Chemother*. 2010; 65(Suppl 4):iv53-iv65.
17. Friedland HD, O'Neal T, Biek D et al. CANVAS 1 and 2: analysis of clinical response at day 3 in two phase 3 trials of ceftaroline fosamil versus vancomycin plus aztreonam in treatment of acute bacterial skin and skin structure infections. *Antimicrob Agents Chemother*. 2012; 56:2231-6.

For complete information about educational activities that are part of this initiative, visit www.ashpadvantage.com/id. There is no charge for the activities, and ASHP membership is not required.

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