Pharmacology Report

Community-Acquired Pneumonia

Treatment Options for Adults

Susan Kleppin, RPh, FASHP

Susan Kleppin, RPh, FASHP, Director of Pharmacy, Chartwell Midwest Wisconsin

Community-acquired pneumonia (CAP) is an acute infection of the lung, particularly areas involving gas exchange, that is acquired in the community, as compared with pneumonia acquired while a patient is hospitalized. Some patients with CAP can be treated safely as outpatients. The decision as to whether a patient with CAP requires hospitalization is guided by the severity of their illness. There are several prediction rules that have been developed to help guide this clinical decision-making.[1]

INCIDENCE AND RISK FACTORS

CAP is the leading cause of infection-disease related death in the United States, with deaths largely occurring in hospitalized patients.[2] At highest risk are children under the age of 5 years, the elderly, and those individuals with comorbidities.[2]

Despite aggressive culturing, less than half of adult patients will have the cause of their CAP identified and respiratory viruses are more commonly isolated than bacteria.[3] The bacteria that most often cause community-acquired bacterial pneumonia (CABP) include *Streptococcus pneumoniae, Haemophilus influenzae, Mycoplasma pneumonia, Staphylococcus aureus, Legionella* species, *Chlamydia pneumoniae,* and *Moraxella catarrhalis.*[4]

INFECTIOUS DISEASES SOCIETY OF AMERICA GUIDELINE FOR TREATMENT OF CAP

In August 2019, the American Thoracic Society and the Infectious Diseases Society of America published a clinical practice guideline outlining evidence-based recommendations for the diagnosis and treatment of CAP in adults.[4] The guideline recognizes that bacterial pathogens often coexist with viruses and that there is no test sensitive enough or fast enough to determine that CAP is caused solely by a virus at the time a patient first presents. Therefore, the recommendations are to initially treat a patient empirically with antibiotics.

The initial recommendations for antibiotic therapy for outpatients with CAP are outlined in Table 1. The recommendations vary depending on whether the patient has any comorbidities and risk factors for infection with methicillin-resistant *Staphylococcal aureus* (MRSA) or *Pseudomonas aeruginosa.* Comorbidities may include chronic heart, lung, liver, or renal disease; diabetes mellitus; alcoholism; malignancy; or asplenia.

RISK FACTORS FOR DRUG-RESISTANT PATHOGENS

The strongest risk factors for infection with *Pseudomonas* or other drug-resistant bacteria are known colonization or past infection with these organisms and hospitalization receiving intravenous (IV) antibiotics within the previous 3 months.[4] If a patient requires hospitalization for CAP, the treatment recommendations in the guideline are stratified by whether the patient has had previous respiratory isolation of MRSA or *P aeruginosa* and if the patient had a recent hospitalization and has risk factors for MRSA or *P aeruginosa* (Table 2).

Patients can also develop drug-resistant *S pneumoniae.* The risk factors in adults include: age >65 years; beta-lactam, macrolide, or fluoroquinolone therapy in the last 3 to 6 months; alcoholism; comorbidities; immunosuppression; or exposure to a child cared for in a daycare center. Another risk factor is previous exposure to a health care setting, such as a hospital or long term care facility.[5] In 2017, there were about 31 000 cases of invasive pneumococcal disease with bacteria resistant to 1 or more antibiotics in 30% of cases.[6] Drug-resistant *S pneumoniae* infections are associated with increased costs,

Author Affiliation: *Chartwell Midwest Wisconsin, Middleton, Wisconsin.*

Susan Kleppin, RPh, FASHP, *is director of pharmacy at Chartwell Midwest Wisconsin.*

The author of this article has no conflicts of interest to disclose.

DOI: 10.1097/NAN.0000000000000378

TABLE 1

Outpatient Antibiotic Recommendations From 2019 ATS/IDSA CAP Guidelines-Initial Treatment[a]

No comorbidities or risk factors for MRSA or *P aeruginosa* (risk factors include previous respirator isolation of MRSA or *P aeruginosa* or recent hospitalization AND receipt of parenteral antibiotics in the last 90 d)	Amoxicillin OR Doxycycline OR Macrolide (if local pneumococcal resistance is <25%)
With comorbidities	Combination therapy with amoxicillin/clavulanate or cephalosporin AND macrolide or doxycycline OR monotherapy with respirator fluoroquinolone

[a]Data from Metlay et al.[4]

Abbreviations: ATS, American Thoracic Society; CAP, community-acquired pneumonia; IDSA, Infectious Diseases Society of America; MRSA, methicillin-resistant *Staphylococcal aureus.*

because patients may experience treatment failures. There is a need for more surveillance, research, and drug development, as well as for more expensive antibiotic therapy.[6]

NEW THERAPEUTIC ALTERNATIVES

Several new antibiotics have been approved in recent years for the treatment of CABP.

Lefamulin

In August 2019, the US Food and Drug Administration (FDA) approved lefamulin, a semisynthetic pleuromutilin indicated for the treatment of CABP. The drug represents the first IV and oral antibiotic with a novel mechanism of action in nearly 20 years.[7] This anti-infective inhibits the 50S ribosomal subunit at the peptidyl transferase center, which inhibits protein synthesis.[8] This is a different target site than other currently marketed protein synthesis inhibitors. This unique mechanism of action is hypothesized to lessen the development of resistance.[7]

Lefamulin has a wide spectrum of activity, including the most common pathogens that cause CABP, including *S pneumoniae, S aureus, H influenzae,* and *M catarrhalis.* It also demonstrates clinical activity against atypical pathogens, including *M pneumoniae, C pneumoniae,* and *L pneumophila.*[7]

In a double-blind clinical trial, patients with pneumonia were randomized to receive IV lefamulin 150 mg every 12 hours or IV moxifloxacin 400 mg every 24 hours. If MRSA was suspected, either linezolid or placebo was added to the moxifloxacin or lefamulin, respectively. After 6 doses, patients could be transitioned to the oral formulation of these drugs. The primary end point (early clinical response

TABLE 2

Inpatient Antibiotic Recommendations from 2019 ATS/IDSA CAP Guidelines by Level of Severity and Risk for Drug Resistance-Initial Treatment[a]

	Standard regimen	Prior respiratory isolation of MRSA	Prior respiratory isolation of *P aeruginosa*	Recent hospitalization and IV antibiotics and risk factors for MRSA	Recent hospitalization and IV antibiotics and risk factors for *P aeruginosa*
Nonsevere inpatient pneumonia	Beta lactam + macrolide OR respiratory fluoroquinolone	Add vancomycin or linezolid and obtain cultures/nasal PCR to allow de-escalation or confirmation of need for continued therapy	Add piperacillin-tazobactam, cefepime, ceftazidime, imipenem, meropenem or aztreonam and obtain cultures to allow de-escalation or confirmation of need for continued therapy	Obtain cultures but withhold MRSA coverage unless results are culture results are positive; if rapid nasal PCR is available, add empiric MRSA therapy if PCR is positive and obtain cultures	Obtain cultures but initiate *P aeruginosa* coverage only if cultures are positive
Severe inpatient pneumonia	Beta lactam + macrolide OR Beta lactam + fluoroquinolone	Add vancomycin or linezolid and obtain cultures/nasal PCR to allow de-escalation or confirmation of need for continued therapy	Add piperacillin-tazobactam, cefepime, ceftazidime, imipenem, meropenem or aztreonam and obtain cultures to allow de-escalation or confirmation of need for continued therapy	Add vancomycin or linezolid and obtain cultures/nasal PCR to allow de-escalation or confirmation of need for continued therapy	Add piperacillin-tazobactam, cefepime, ceftazidime, imipenem, meropenem or aztreonam and obtain cultures to allow de-escalation or confirmation of need for continued therapy

[a]Data from Metlay et al.[4]

Abbreviations: ATS, American Thoracic Society; CAP, community-acquired pneumonia; IDSA, Infectious Diseases Society of America; IV, intravenous; MRSA, methicillin-resistant *Staphylococcal aureus*; PCR, polymerase chain reaction.

at 96 ± 24 hours) occurred in 87.3% of patients taking lefamulin (n = 276) and 90.2% of patients taking moxifloxacin (n = 275), indicating that lefamulin is noninferior to moxifloxacin in this patient population.[7]

The most common adverse effects reported include nausea, insomnia, injection site pain, alanine transaminase elevation, and diarrhea. Prolonged QT intervals occurred rarely in study subjects, but lefamulin should be avoided in patients with known QT prolongation and ventricular arrhythmias.[9]

The recommended adult IV dose is 150 mg every 12 hours administered as an infusion over 60 minutes for 5 to 7 days. The recommended oral dose is 600 mg every 12 hours for a duration of 5 days.[9]

Omadacycline

The FDA approved omadacycline for the treatment of CAP in October 2018. A tetracycline-class antibiotic, the drug has in vitro activity against common atypical and typical CAP pathogens, including *S pneumoniae, H influenzae, S aureus, Legionella pneumophila, M pneumoniae,* and *C pneumoniae.*[10] In a double-blind, double-dummy, randomized noninferiority trial, patients were randomized to receive omadacycline (100 mg IV every 12 hours × 2 doses, then every 24 hours) or moxifloxacin (400 mg IV every 24 hours). On the third day, there was an option to transition to the oral formulation of these drugs. The primary efficacy end point was early clinical response and no worsening of symptoms at 72 to 120 hours.[10] Omadacycline was found to be noninferior to moxifloxacin for early clinical response (81.1% and 82.7%, respectively).

The most common adverse effects reported include alanine aminotransferase elevation, hypertension, gamma-glutamyltransferase elevation, insomnia, vomiting, constipation, and nausea.[11] Recommended adult dosing is an IV loading dose of 200 mg over 60 minutes, followed by 100 mg IV daily over 30 minutes or 300 mg orally daily for 7 to 14 days.[11]

Delafloxacin

Delafloxacin, a fluoroquinolone, was initially approve in 2017 for the treatment of acute bacterial skin and soft tissue infections. Now approved for the treatment of CAP, delafloxacin has activity against *S pneumoniae, S aureus, Klebsiella pneumoniae, Escherichia coli, P aeruginosa, H influenzae, Haemophilus parainfluenzae, Chlamydia pneumonia, L pneumophila,* and *Mycoplasma pneumoniae.*[12]

A randomized, double-blind, comparator-controlled phase 3 drug study was conducted to compare the efficacy and safety of delafloxacin 300 mg IV twice daily or moxifloxacin 400 mg IV once daily in adults with CABP.[13] The primary end point was early clinical response, defined as improvement at 96 ± 24 hours after the first dose of the study drug. A transition to oral doses was allowed after a minimum of 6 IV doses. The total duration of treatment was 5 to 10 days. The early clinical response rate for the delafloxacin group was 88.95% compared to 89.00% in the moxifloxacin group, demonstrating the noninferiority of delafloxacin to moxifloxacin in the treatment of CAP.

The most common adverse events reported in patients treated with delafloxacin were nausea, diarrhea, headache, transaminase elevations, and vomiting.[12]

Like other fluoroquinolones, the labeling of delafloxacin contains warnings about the risks of serious adverse effects such as tendon rupture, peripheral neuropathy, and central nervous system disturbances.[14] Structural differences in the delafloxacin molecule as compared with the other fluoroquinolones seem to reduce the incidence of phototoxicity. The incidence of QTc prolongation associated with the use of delafloxacin also has been reported to be less than experienced with other fluoroquinolones.[14]

Recommended dosing for the treatment of CAP in adults is 300 mg IV every 12 hours over 60 minutes or 450 mg orally every 12 hours for 5 to 10 days.[12]

All 3 of these antimicrobial agents are treatment options for CAP, but because of the limited clinical experience with these agents, they should be reserved for patients with severe CAP with resistant organisms. The cost of these agents is also significant as compared with the standard of care, which supports restriction to clinical situations where alternative treatments are not available or where adverse effects necessitate the use of 1 of these novel agents. A comparison of these agents, including average wholesale price, can be found in Table 3.

CONCLUSION

CAP is a common and potentially serious illness. It is associated with significant morbidity and mortality in adults, especially in patients over the age of 65 years and those

TABLE 3

Comparison of New Agents for the Treatment of Community-Acquired Pneumonia

	Efficacy	Activity for resistant Pneumococcus?	AWP[a] for 6-d course
Omadacycline 200 mg IV × 1 dose then either 100 mg IV q24h or 200 mg PO q24h	All noninferior to moxifloxacin	Yes	IV/PO: ~$2898
Lefamulin IV: 150 mg q12h PO: 600 mg q12h		Yes	IV $1476 PO $1980
Delafloxacin IV: 300 mg q12h PO: 450 mg q12h		Yes	IV: $1908 PO: $1021
In comparison, ceftriaxone 2 g IV q24h + azithromycin 6-day course, AWP (range) $8-$667.			

[a]AWP, average wholesale price, as of January 24, 2020.
Abbreviations: IV, intravenous; PO, by mouth; q, every.

with comorbidities. Clinical treatment guidelines from the American Thoracic Society/Infectious Diseases Society of America are available to guide diagnosis and treatment of CAP. Several new antimicrobial agents have come to market in the last several years that hold promise in the treatment of CAP secondary to drug-resistant *S pneumoniae,* but more clinical experience is needed with these agents.

REFERENCES

1. Marrie TJ, Shariatzadeh MR. Community-acquired pneumonia requiring admission to an intensive care unit: a descriptive study. *Medicine*. 2007;86(2):103-111. doi: 10.1097/MD.0b013e3180421c16
2. Ramirez JA, Wiemken TL, Peyrani P, et al. Adults hospitalized with pneumonia in the United States: incidence, epidemiology, and mortality. *Clin Infect Dis*. 2017;65(11):1806-1812. doi: 10.1093/cid/cix647
3. Jain S, Self WH, Wunderink RG, et al. Community-acquired pneumonia requiring hospitalization among U.S. adults. *N Engl J Med*. 2017;373(5):415-427. doi: 10.1056/NEJMos1500245
4. Metlay JP, Waterer GW, Long AC, et al. Diagnosis and treatment of adults with community-acquired pneumonia: an official clinical practice guideline of the American Thoracic Society and Infectious Diseases Society of America. *Am J Respir Crit Care Med*. 2019;200(7):e45-e67. doi:10/1164/rccm201908-1581ST
5. Kuster SP, Rudnick W, Shigyeva A, et al. Previous antibiotic exposure and antimicrobial resistance in invasive pneumococcal disease: results from prospective surveillance. *Clin Infect Dis*. 2014;59(7):944-952. doi: 10.1093/cid/ciu497
6. Centers for Disease Control and Prevention. Pneumococcal disease–drug resistance. Updated September 7, 2017. Accessed January 13, 2020. https://www.cdc.gov/pneumococcal/drug-resistance.html
7. File TM, Goldberg L, Das A, et al. Efficacy and safety of intravenous-to-oral lefamulin, a pleuromutilin antibiotic, for the treatment of community-acquired bacterial pneumonia: the Phase III lefamulin evaluation against pneumonia (LEAP 1) trial. *Clin Infect Dis*. 2110;69(11):1865-1867. doi: 10.1093/cid/ciz090
8. Rodvold KA. Introduction: lefamulin and pharmacokinetic/pharmacodynamic rationale to support the dose selection of lefamulin. *J Antimicrob Chemother*. 2019;74(Suppl_3):iil2-iii4. doi: 10.1093/jac/dkz084
9. XENLATA™ *(lefamulin)*. Package insert. Nabriva Therapeutics; 2019.
10. Stets R, Popescu M, Gonong JR, et al. Omadacycline for community-acquired bacterial pneumonia. *N Engl J Med*. 2019;380(6):517-527. doi: 10/1056/NEJMoa1800201
11. NUZYRA® *(omadacylcine)*. Package insert. Paratek Pharmaceuticals, Inc; 2020.
12. Baxdela® *(delafloxacin)*. Package insert. Melinta Therapeutics, Inc; 2019.
13. Horcajada JP, Salata RA, Alvarez-Sala R, et al. A Phase 3 study to compare delafloxacin with moxifloxacin for the treatment of adults with community-acquired bacterial pneumonia (DEFINE-CABP). *Open Forum Infect Dis*. 2020;7(1):ofz514. doi:10/1093/ofid/ofz514
14. Jorgensen SC, Mercuro NJ, Davis SL, Rybak MJ. Delafloxacin: place in therapy and review of bicrobiologic, clinical and pharmacologic properties. *Infect Dis Ther*. 2018;7(2):197-217. doi: 10/1007/s40121-018-0198-x