Community-acquired pneumonia: a US perspective on the guideline gap

Maricar Malinis 1, Lilian Abbo2, Jose A. Vazquez3 and Luis Ostrosky-Zeichner4

1Yale School of Medicine, Yale University, New Haven, CT, USA; 2Miller School of Medicine, University of Miami, Miami, FL, USA; 3Medical College of Georgia, Augusta University, Augusta, GA, USA; 4McGovern Medical School, University of Texas Health Science Center at Houston, Houston, TX, USA

*Corresponding author. E-mail: Luis.Ostrosky-Zeichner@uth.tmc.edu
@DrLuisO, @Maricar_Malinis, @LiliAbbo, @Dr_joeID

Received 10 October 2023; accepted 6 February 2024

Community-acquired pneumonia continues to be one of the most common causes of morbidity and mortality due to infectious disease. The aetiologies, clinical presentations, diagnostic modalities and therapeutic options are changing and outpacing the creation of management guidelines. This educational article summarizes a roundtable activity sponsored by an unrestricted educational grant by Paratek that included US experts discussing these changes and identifying gaps in the current guidelines.

© The Author(s) 2024. Published by Oxford University Press on behalf of British Society for Antimicrobial Chemotherapy. This is an Open Access article distributed under the terms of the Creative Commons Attribution-NonCommercial License (https://creativecommons.org/licenses/by-nc/4.0/), which permits non-commercial re-use, distribution, and reproduction in any medium, provided the original work is properly cited. For commercial re-use, please contact reprints@oup.com for reprints and translation rights for reprints. All other permissions can be obtained through our RightsLink service via the Permissions link on the article page on our site—for further information please contact journals.permissions@oup.com.

New trends in the epidemiology of community-acquired pneumonia (CAP)

CAP continues to be one of the most common causes of morbidity and mortality due to infectious disease in all patients. Despite the COVID-19 pandemic, it continues to be a neglected, but common infection. Interestingly, there is a lack of urgency and disease awareness when one discusses CAP, perhaps because of its commonly used term ‘walking pneumonia’, not realizing that the mortality associated with CAP remains between 10% and 20%.1 According to the American Thoracic Society (ATS)/IDSA guidelines from 2019, CAP continues to be a growing health problem globally, with an annual global burden of approximately 350 million cases in 2016.2 In the USA, there are over 1 million hospitalizations due to CAP per year, not including those associated with SARS-CoV-2.3

Recent changes in the microbial aetiology of CAP

There are several challenges that remain when discussing the evolving epidemiology of CAP in the USA. The most important of these is being the increase in the number of pathogens that are now routinely diagnosed in patients with CAP. This is especially true for the viral causes of pneumonia such as SARS-CoV-2, respiratory syncytial virus and human metapneumovirus. In addition, certain fungal infections such as Histoplasma capsulatum and Coccidioides immitis are also increasing in frequency as causes of non-bacterial CAP in endemic areas. Finally, it is important to point out that in the past 12–24 months there has been an increase in Mycobacterium tuberculosis, especially in the southwest part of the USA. This is possibly due to the large migration of individuals.4

Overall, bacterial and viral organisms constitute the most common causes of CAP. Pathogens such as Streptococcus pneumoniae and Haemophilus influenzae continue to be the most common bacterial pathogens recovered from sputum and occasionally, the bloodstream. However, more recently we are seeing an increase in CAP due to Staphylococcus aureus and Klebsiella pneumoniae. In addition, the intracellular pathogens or ‘atypical pneumonias’ frequently constitute up to 30% of...
The term which included 24 pro-founding increased mortality among patients meeting the criteria for HCAP but associated it with the patient’s comorbidities rather than the presence of an MDRO. A meta-analysis and systematic review, which included 24 prospective and retrospective studies, found that guideline-defined HCAP did not accurately identify resistant pathogens, nor did it determine mortality risk with the presence of an MDRO. The accompanying editorial commented that HCAP criteria may not accurately identify risk for MDROs due to the diversity of pathogens across the healthcare system and the different antibiotic policies from country to country. Finally, a Veterans Affairs (VA)-based study also reported that guideline-concordant therapy in non-severe HCAP patients did not improve overall survival.

The 2019 guideline did comment on possibly ‘moving away’ from the HCAP definition and its management as it has caused the overuse of broad-spectrum antibiotics. Therefore the term HCAP is broadly now in disuse and the preferred approach is individualized risk for MDROs based on local epidemiology. An effort to perform an appropriate collection of respiratory cultures (and/or blood cultures) at the time of diagnosis of pneumonia (i.e. within 48–72 h) will improve the yield of cultures. Newer studies involving multiplex PCR can expedite diagnosis. Appropriate modification of antibiotics based on microbiological data can help reduce prolonged broad-spectrum antibiotic exposure.

**Risk factors and clinical presentation**

Established risk factors for CAP include older age, chronic comorbidities, viral infection, impaired airway protection (i.e. increased risk for microaspiration), smoking and environmental exposure (water, animal, toxin exposures). Over the years, novel risk factors for CAP have emerged, and these mainly involve the use of immunosuppressive therapies in the treatment of chronic diseases. For example, anti-TNF antibodies, ibrutinib and B-cell depleting agents increase the risk for infections due to non-tuberculous mycobacteria, Aspergillus spp. and respiratory viruses, respectively. Globalization and immigration play a considerable role in the transmission of respiratory infections. In the last 3 years, we have witnessed a novel virus (SARS-CoV-2) emerging, and certain host factors predispose to severe disease, such as older age, high BMI, socioeconomic background, race, and sex.

The clinical presentation of CAP can range from mild disease characterized by fever, cough and dyspnea to severe disease characterized by sepsis and respiratory failure. Symptom severity highly depends on pathogen virulence, the burden of exposure, and the host’s immune response. Signs and symptoms of pneumonia may be subtle among patients with advanced age and/or impaired immune systems. Notably, chest radiographs may be poorly sensitive and not able to detect evidence of pneumonia in individuals with impaired immunity. Hence, other radiographical modalities, such as CT scan of the chest, may have improved sensitivity in demonstrating abnormal lung findings. It is essential to highlight that with COVID-19, atypical presentations such as anosmia, dysgeusia, dermatological findings (maculopapular rash, vesicular eruptions, reddish nodules), conjunctivitis, gastrointestinal symptoms and thromboembolic complications have been reported.

**CAP versus healthcare-associated pneumonia: a blurring distinction and term in disuse**

Per the definition in the 2005 ATS/IDSA guideline, healthcare-associated pneumonia (HCAP) is a pneumonia in non-hospitalized patients with significant healthcare system experience that predisposes an individual to increased risk for MDR organism (MDRO) infection. These risk factors include prior hospitalization for at least 2 days in the preceding 90 days, residence in a nursing home or long-term care facility, interventions such as home infusion therapy, chronic dialysis, home wound care and exposure to family members with MDRO infection. The landmark study of Kollef et al. that defined HCAP involved a large US inpatient database demonstrating higher rates of MDRO (mainly MRSA, Pseudomonas and Enterobacter) amongst patients meeting the HCAP criteria of the study and was associated with increased mortality. However, since then, several studies have evaluated the validity of that report. The study by Chalmers et al. found increased mortality among patients meeting the criteria for HCAP but associated it with the patient’s comorbidities rather than the presence of an MDRO. A meta-analysis and systematic review, which included 24 prospective and retrospective studies, found that guideline-defined HCAP did not accurately identify resistant pathogens, nor did it determine mortality risk with the presence of an MDRO. The accompanying editorial commented that HCAP criteria may not accurately identify risk for MDROs due to the diversity of pathogens across the healthcare system and the different antibiotic policies from country to country. Finally, a Veterans Affairs (VA)-based study also reported that guideline-concordant therapy in non-severe HCAP patients did not improve overall survival.

**Novel therapeutics for CAP**

**Adjuvant therapeutics for CAP**

Adjuvant therapy has generally been relegated to supportive therapy, but a recent breakthrough study found that adding hydrocortisone to antibiotics in the setting of severe CAP was associated with decreased risk of mortality by Day 28, therefore this intervention is likely to become standard of care.

**Omadacycline** is a tetracycline antibiotic and was approved in 2018 for treatment of bacterial CAP (CABP). It overcomes the resistance by tetracycline efflux and ribosomal protection mechanisms and has activity against Legionella pneumophila, M. pneumoniae and C. pneumoniae. Thus, it can be used as a single agent to treat CABP as an alternative to the empirical combination of a β-lactam and a macrolide. The efficacy and safety of omadacycline were tested on a Phase III randomized control trial (OPTIC) comparing omadacycline in 388 patients with moxifloxacin in 386 patients with CABP followed by oral omadacycline or moxifloxacin. The early clinical response was 81.1% in the omadacycline group compared with 82.7% in the comparator group. In the post-treatment evaluation, clinical response rate was 87.6% in the omadacycline arm compared with 85.1% in the moxifloxacin arm. The rate of adverse events leading to treatment discontinuation was 5.5% with omadacycline compared with 7% with moxifloxacin.

**Lefamulin** is a novel pleuromutilin antibiotic and was approved in August 2019 by the US FDA for use in CABP. Lefamulin inhibits protein synthesis by inhibition of the 50S bacterial ribosome. It has activity against S. pneumoniae, MRSA, VRE, MDR Neisseria gonorrhoeae, C. pneumoniae, L. pneumophila, M. pneumoniae and H. influenzae. Lefamulin exhibits time-dependent killing, with higher concentrations in epithelial lining fluid than in plasma. Lefamulin was non-inferior to moxifloxacin in 551 adults with CABP in a Phase III (LEAP-1) clinical trial. Early
clinical response was 87.3% versus 90.2%. The rate of drug discontinuation was 2.9% in the lefamulin arm and 4.4% in the moxifloxacin arm. In the second Phase III clinical trial (LEAP-2), oral lefamulin was compared with moxifloxacin in 738 patients with CABP. Lefamulin was non-inferior to moxifloxacin for CABP (90.8% versus 90.8%), clinical response (87.5% versus 89.1%) and clinically evaluable population (89.7% versus 93.6%).

Cefiderocol is the first in a class of siderophore cephalosporins with activity against ESBL- and carbapenemase-producing Gram-negative bacteria (carbapenem-resistant Enterobacteriales, carbapenem-resistant Pseudomonas aeruginosa and carbapenem-resistant Acinetobacter baumannii), MDR Stenotrophomonas maltophilia and Burkholderia cepacia. Potential indications include complicated urinary tract infection, healthcare-associated pneumonia/ventilator-associated pneumonia, bloodstream infection and sepsis caused by MDR Gram-negative isolates. It is a potent broad-spectrum agent that is not routinely recommended for first-line CAP treatment unless there is clinical failure to first-line therapy, in addition to other factors for MDROs.

Solithromycin is a novel, fourth-generation macrolide, known as a fluoroketolide, which inhibits protein synthesis by binding to the bacterial ribosome. It has activity against macrolide-resistant S. pneumoniae, H. influenzae and atypical pathogens, with potential indication for use in CABP. Oral solithromycin was non-inferior to oral moxifloxacin in 860 adults with CABP in a Phase III trial (SOLITAIRE-ORAL). Early clinical response was 78.2% versus 77.9%. Elevation of ALT was observed in 5.4% of the solithromycin group (SOLITAIRE-ORAL). Early clinical response was 78.2% versus 77.9%.


