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Community-acquired pneumonia: The importance of the early detection of drug-resistant organisms

Doppalapudi *Set al.* Detection of drug-resistant organisms

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Abstract

Pneumonia is a disease associated with significant healthcare burden with over 1.5 million hospitalizations annually and is the eighth leading cause of death in the United States. While community-acquired pneumonia (CAP) is generally considered an acute time-limited illness, it is associated with high long-term mortality, with nearly one-third of patients requiring hospitalization dying within one year. An increasing trend of detecting multidrug-resistant (MDR) organisms causing CAP has been observed, especially in the Western world. In this editorial, we discuss about a publication by Jatteppanavar B et al. which reported that a case of a MDR organism was the culprit in developing pneumonia, bacteremia, and infective endocarditis that led to the patient's death. The early detection of these resistant organisms helps improve patient outcomes. Significant advances have been made in the biotechnological and research space, but preventive measures, diagnostic techniques, and treatment strategies need to be developed.

Key words: Methicillin-resistant *Staphylococcus aureus*; Polymerase chain reaction; Antibiotic resistance; Bacterial colonization

Core tip:

This editorial focuses on community-acquired pneumonia (CAP) and the importance of the early detection of drug-resistant organisms. CAP is considered an acute time-limited illness and is associated with high long-term mortality, with nearly one-third of patients requiring hospitalization dying within one year. There is an increasing trend of detecting multidrug-resistant (MDR) organisms causing CAP especially in the Western world. It has been shown that the early detection of these resistant organisms helps improve patient outcomes. Moreover, significant advances have been made in the biotechnological and research space, but preventive measures, diagnostic techniques, and treatment strategies need to be further developed.

INTRODUCTION

Pneumonia is a disease associated with a high risk of morbidity and mortality worldwide and is increasing in prevalence with age. Pneumonia is an unusual outcome of familiar host-microbe interactions and is defined as an acute infection of the pulmonary parenchyma leading to host immune function disarray and organism invasion. The American Thoracic Society (ATS)/Infectious Diseases Society of America categorizes pneumonia based on the site of acquisition as CAP and hospital-acquired pneumonia (HAP). Healthcare-associated pneumonia (HCAP), now an obsolete term, was previously used to address patients at risk for MDR pathogens associated with healthcare facilities^[1-3]. This term led to the inappropriate usage of broad-spectrum antibiotics. CAP is an acute infection of the pulmonary parenchyma that is acquired outside healthcare facilities and is one of the leading infectious cause of hospitalizations and death in the United States. HAP are infections that occur after 48 h of admission. Antibiotic-resistant bacteria are a well-known cause of nosocomial pneumonia. However, a steady rise in cases of CAP caused by MDR pathogens has been observed. The United States Centers for Disease Control and Prevention and the European Centre for Disease Prevention and Control termed MDR organisms as acquired nonsusceptibility to a minimum of one drug in three or more antimicrobial classes^[1]. Moreover, the term “extensively drug-resistant” (XDR) is defined as nonsusceptibility to at least one drug in all but two antimicrobial classes. Finally, pan-drug resistance is defined as nonsusceptibility to drugs of all antimicrobial classes. *Streptococcus pneumoniae* is considered the most common causative pathogen for pneumonia, although a steady decline in its prevalence has been observed since the widespread use of pneumococcal vaccination and herd immunity^[2]. *Hemophilus influenzae* and *Legionella* species join pneumococcus as the most common causes of CAP requiring admissions. However, a trend of organisms that were traditionally associated with the healthcare setting now presenting in adults from the community has been observed. Organisms, such as *Pseudomonas aeruginosa*, extended-spectrum beta-

lactamase-producing *Enterobacteriaceae*, and methicillin-resistant *Staphylococcus aureus* (MRSA) are now increasingly isolated from community residents^[3]. Early adequate empirical antimicrobial treatment is the cornerstone of survival in patients with pneumonia. However, the delay in obtaining the susceptibility of the isolates and changes in antimicrobial resistance patterns make it difficult to choose the appropriate antimicrobial agents. The importance of early appropriate antibiotics has long been established in multiple studies on infectious processes, including pneumonias, intra-abdominal infections, and bacteremia. The retrospective cross-sectional study of Tetsu et al. showed that the receipt of appropriate initial empiric antibiotic therapy was associated with lower in-hospital mortality^[4]. The outcomes of patients that switched from inappropriate to appropriate therapy were better than those of patients who remained to undergo inappropriate therapy. However, the benefit was not as significant as that for those who were initially started on appropriate therapy. Jatteppanavar B et al^[5] presented an important case of a previously healthy young man who presented with fever, abdominal pain, vomiting, and rash. Studies have revealed MDR pneumonia along with bacteremia and infective endocarditis with cultures containing MRSA and *Pseudomonas*^[5].

Serious infections caused by MRSA have been increasing worldwide, especially in Western countries. The current standard of practice for the identification of bacteria causing pneumonia are Gram staining and semiquantitative conventional cultures from direct respiratory sputum samples. The identification of bacteria is based on matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOF MS)^[6] and susceptibility testing. Due to the average time needed for microbial diagnosis and susceptibilities, many patients admitted to the hospital may not receive the appropriate initial treatment^[7,8]. The process for speciation and susceptibility takes approximately 48 hours and comes with low sensitivity, commonly if the specimen was taken after the initiation of antibiotics. Moreover, it is difficult to differentiate the identified organism between a colonizer and infection. Consequently, patients may receive inappropriate antibiotic treatment, which may lead to adverse outcomes^[8].

Jatteppanavar et al^[5] also encountered a similar challenge in the management of their patients. Their case also confirmed the low sensitivity of MALDI-TOF through a positive multiplex polymerase chain reaction (PCR) test (BioFire) of a respiratory specimen but with negative growth when attempting incubation.

Advances in the early screening methods with molecular techniques using multiplex PCR in the last decade have helped to rapidly identify microorganisms^[9]. The challenge remains in the detection of its drug susceptibilities. Although some platforms use rapid molecular techniques to detect some resistance genes and phenotyping, these methods are less sensitive for Gram negatives because they use different resistance mechanisms simultaneously. One of the earlier studies signifying the importance of the early detection of drug-resistant organisms with PCR was performed by Peiffer-Smadja et al.^[10,11] They showed that multiplex PCR helps improve empiric antibiotic therapy in 63% of patients admitted with pneumonia. Multiplex PCRs provided good overall performance for bacterial identification (80% sensitivity, 95% confidence interval [CI] 71–88%, 99% specificity, 95% CI 99–100%) and resistance gene detection^[10,11]. A potential problem with these rapid diagnostic tests could be ⁹ an increased detection rate of common colonizers of the upper respiratory tract, in particular *H. influenzae* and *S. aureus*. Finally, nasal swab MRSA PCR test has been shown to be the preferred ⁸ screening tool in predicting the regimen of empiric antibiotics. This test showed a sensitivity of 88.0%, specificity of 90.1%, positive predictive value of 35.4%, and negative predictive value of 99.2%^[12-14]. With ⁸ the increasing prevalence of community-acquired MRSA infections, this tool may play a role in pneumonia care. Resistance to antibiotics is becoming an alarming problem, and treatment failures add to the already high morbidity and mortality associated with pneumonia. The most common mechanisms for antibiotic resistance are altered drug targets, enzymatic drug inactivation, altered drug accessibility, and increased efflux of antimicrobial compounds^[15]. *Staphylococcus aureus* confers its resistance to methicillin by acquiring a gene encoding a penicillin-binding protein (PBP2a), which lowers its affinity to beta-

lactams^[15]. This resistance allows MRSA to continue its cell wall biosynthesis, despite the presence of typical inhibitory concentrations of antibiotics.

Several scoring systems have been developed to help identify those at risk of MDR CAP. Of the following two systems, the clinical scores by Shorr et al.^[16] and Aliberti et al.^[17] categorize the various risk factors into categories. In the system designed by Shorr et al.^[16], points are assigned for the recent hospitalization, nursing home residence, hemodialysis, and intensive care unit admission. On the other hand, the system designed by Aliberti et al.^[17] assigns points to hospitalized patients with CAP with chronic renal failure, prior hospitalizations, residence in a nursing home, and a few other risk factors. Several prospective scoring systems have been developed but require further external validation because most studies confirming their reliability were conducted in limited populations. Further research is needed to confirm the utility of these risk scores, including identifying patients that are likely to respond to specific treatments and have a lower mortality rate when these risk scores are used.

Vancomycin, which was invented over 50 years ago, is considered the first-line antibiotic used for treating MRSA infections. It acts by targeting the cell wall by disrupting its peptidoglycan assembly. Alternatives with different mechanisms of action include daptomycin, linezolid, tigecycline, dalbavancin, temafloxacin, and ceftaroline. Alternative avenues for treatment strategies have been further investigated, including but not limited to antibodies, antiviral therapy, bacteriophages, and vaccines. Two types of antibodies have been studied: those that bind to the pathogen to promote opsonization-mediated phagocytosis and those that neutralize virulence factors, such as toxins. In antivirulence therapy, the strategy is to disarm the key virulence factors involved in disease progression, allowing clearance by a functional immune system^[18-21].

In conclusion, MDR pneumonia is associated with increased morbidity and mortality. Early recognition and treatment with appropriate antibiotics are associated with prolonged survival. Advancements have also been made in the identification of organisms and their resistance patterns. Microbial DNA sequencing, M-PCR, and the

BioFire panel have been used to detect bacterial pneumonia in a quick turnaround time. Novel PCR-based techniques may play a significant role in the early discovery of drug-resistant genes that can help to overcome the spread of these multidrug-resistant genes between bacteria. However, the current biomolecular panels available for detection of respiratory pathogens lack sensitivity and are not available for all MDR bacteria. Therefore, future research is needed to develop alternative methods for identification of these MDR bacteria and investigate newer and effectual combination therapies that can both minimize side effects and strengthen activity against drug-resistant genes.

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