

UNDERSTANDING COMMUNITY -ACQUIRED RESPIRATORY TRACT INFECTIONS: NEW CONCEPTS OF DISEASE PATHOGENESIS AND NEW MANAGEMENT STRATEGIES

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In this issue of Current Opinion in Pulmonary Medicine, we focus on the problem of community-acquired lower respiratory tract infections. It is very clear from the discussions in this monograph, that clinical and basic research have translated into tangible ways to improve outcomes for our patients. This has spanned the problems of community acquired pneumonia (CAP) and acute exacerbations of chronic obstructive pulmonary disease (AECOPD), and has included interventions from surveillance to specific antimicrobial therapies to vaccines for prevention. Epidemiologic studies have focused our attention on unexpected complications of lung infection, such as acute cardiac disease, and observational and interventional studies have suggested ways to improve outcomes, such as mortality and readmission to the hospital.

One of the most revolutionary advances in the field of lung infection is the realization that the normal lower respiratory tract is not sterile, and that it is inhabited by a "microbiome" of organisms that is more diverse and numerous than ever imagined (1). With the advent of new molecular methods, it is very clear that our understanding of the organisms that contribute to illness, which has been dependent on standard culture techniques, is incomplete. The presence of the RNA of millions of bacteria, from hundreds of species, is a revolutionary finding in both healthy and infected patients. We are just beginning to understand how the microbiome changes in the presence of acute illness, and this understanding is likely to lead to new concepts of disease pathogenesis and new therapeutic approaches. Dy and Sethi have examined the role of the microbiome in AECOPD (2). They discuss the association of loss in microbiome diversity with disease severity. They also report changes in the microbiome with smoking, COPD severity, acute exacerbation, and therapy with steroids and antibiotics. This is an exciting and evolving field, that may change our understanding of lung infections and the best way for treating AECOPD.

Maeurer and colleagues demonstrate how an understanding of host defense mechanisms can lead to novel directions for the therapy of antimicrobial resistant bacterial, fungal and viral infections, that are not easily treated by currently available agents (3). They nicely outline specific cytokine responses to a wide range of pathogens, which could be amenable to future

interventions. For example, new host-directed therapies could be emerging with agents such as alpha-1-antitrypsin, bone marrow-derived stem cells, specially activated T cells, novel kinase inhibitors, and pathogen-specific monoclonal antibodies.

We have begun to appreciate that CAP has both short-term and long-term mortality, and that its impact is as more than just as an acute illness. One factor that may contribute to adverse outcomes, both acutely and after pneumonia resolution, is the development of ischemic and arrhythmic cardiac disease. Rae and colleagues review new information about the association of CAP and cardiac complications, reporting that up to one-third of CAP patients may experience cardiovascular complications within 30 days of hospital admission (4). These complications include acute myocardial infarction, arrhythmias and congestive heart failure. Quite surprisingly, the risk may persist for at least 1 year after pneumonia, and maybe for as long as 10 years. The mechanisms are being elucidated, but can include direct invasion of the myocardium by organisms such as pneumococcus. Based on these findings, strategies to prevent CAP, may soon be viewed as cardioprotective interventions.

One of the first steps to improving CAP management, is to recognize which patients are at risk for infection with multidrug-resistant (MDR) pathogens. Although CAP has traditionally been an infection caused by pneumococcus and other easily treated pathogens, the patients who are now affected, are increasingly complex, and moving freely between the community, healthcare centers, nursing homes and hospitals, and these exposures add to the risk of infection with MDR pathogens. Sibilia et al have discussed the challenges associated with identifying patients coming from the community who are at risk for MDR pathogen pneumonia (5). They discuss the potential problems with the concept of healthcare associated pneumonia, and review risk factors for infection with MDR pathogens. These risk factors include: prior hospitalization, hemodialysis, home wound care, residence in a nursing home, home infusion therapy, recent antibiotics, immune suppression, tube feeding, aspiration, poor functional status, and prior infection with an MDR pathogen. The current challenge is to develop a method to rapidly identify these patients, and Sibilia and colleagues review scoring systems that have been developed for this purpose. One unresolved challenge is whether we will be able to use

epidemiologic data to identify risks for specific pathogens such as methicillin-resistant *S. aureus* and *P. aeruginosa*, or whether the risk factors will just be able to tell us that any of these organisms are possible. It is likely that we will need to combine both epidemiologic data and rapid molecular diagnostics, to optimize the identification of patients at risk for infection with MDR pathogens, but these efforts could lead to improvements in the selection of appropriate and focused empiric therapy.

The most important pathogen causing CAP is *Streptococcus pneumoniae*, or pneumococcus, and it too is becoming increasingly resistant to commonly used antibiotics such as the penicillins and macrolides. Cilloniz and colleagues have reviewed this problem and provided a look at the incidence and clinical impact of drug-resistant pneumococcus (DRSP) (6). They have reported the risks factors for DRSP and have shown how its presence may alter the clinical presentation of pneumonia. While the implications for therapy are still evolving, it is clear that our focus needs to be on using antibiotics in a way that will halt the development of even more resistance. In addition, they point out the double-edged sword of using vaccines for prevention. The older pneumococcal conjugate vaccines have led to the emergence of virulent "replacement strains" , while the newer, more broad conjugate vaccines may have a large and beneficial impact on the future incidence of pneumococcal pneumonia, and resistance.

One clear benefit from our enhanced understanding of CAP is the possibility of improving outcomes for our patients, a topic which Bender and Niederman have reviewed (7). Strategies to achieve this include a renewed focus on the site of care decision, recognizing the adverse impact of delayed intubation and delayed admission to the ICU. An awareness of the cardiac complications of CAP, may mandate a reconsideration of the need for cardiac monitoring in selected patients. Severity scoring systems and biomarkers may also help with the site of care decision. Therapy choices are also important contributors to outcome, including the benefits that can come from the use of adjunctive empiric macrolide therapy for severely ill patients, the reduced mortality with the use of anti-toxin therapy for community acquired methicillin resistant *S. aureus* infection, and the potential benefit of adjunctive corticosteroids for selected patients with severe CAP. Finally, they point out the importance of managing the

comorbid illnesses that are common in CAP patients, with the benefits of improving mortality and avoiding readmission to the hospital.

This issue of Current Opinion in Pulmonary Medicine is an exciting one, and it illustrates the current state of knowledge in community acquired respiratory tract infections. Many recent observations have led to changes in patient management that are able to benefit our patients today. At the same time, novel and exciting developments in the basic biology of host defenses and bacterial pathogenesis are pointing to where future advances will emerge. We are deeply grateful to the authors of this issue, and hope that their discussions will stimulate further advances in the understanding and management of these challenging infections.

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