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Community-Acquired Pneumonia
Pathogenesis of Acute Cardiac Events and Potential Adjunctive Therapies

Charles Feldman, MBBCh, DSc, FCCP; and Ronald Anderson, PhD

Despite advances in antimicrobial chemotherapy and access to sophisticated intensive care facilities, bacterial community-acquired pneumonia (CAP) continues to carry an unacceptably high mortality rate of 10% to 15% in hospitalized cases. CAP, considered by many to be the most underestimated disease worldwide, poses a particular threat to the elderly whose numbers are steadily increasing in developed countries. Indeed, elderly patients with severe CAP, as well as those with other risk factors, are at significant risk for development of inflammation-mediated acute cardiac events that may undermine the success of antimicrobial therapy. Adjunctive antiinflammatory strategies are, therefore, of considerable potential benefit in this setting. Currently, the most promising of these are the macrolides, corticosteroids, and, more recently, statins, all of which target immune/inflammatory cells. In addition, recent insights into the immunopathogenesis of acute coronary events in patients with CAP have revealed a probable pivotal role of platelet activation, potentially modifiable by agents that possess anti-inflammatory or platelet-targeted activities or both. Statins, which not only possess anti-inflammatory activity but also appear to target several pathways involved in platelet activation, seem particularly well suited as adjuncts to antibiotic therapy in bacterial CAP. Following a brief consideration of the immunopathogenesis of bacterial CAP, this review is focused on mechanisms of platelet activation by CAP pathogens, as well as the pharmacologic control thereof, with emphasis on statins.

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ABBREVIATIONS: ADP = adenosine diphosphate; CAP = community-acquired pneumonia; CD40L = CD40 ligand; GP = glycoprotein; GPCR = G-protein-coupled receptor; ICAM = intercellular adhesion molecule; LOX = lectin-like oxidized low-density lipoprotein-1 receptor; NF-κB = nuclear factor κB; NOD = nucleotide-binding oligomerization domain; PAF = platelet-activating factor; PF4 = platelet factor-4; TLR = Toll-like receptor; TP = thromboxane; TxA_2 = thromboxane A_2

Despite years of intensive investigation into various aspects of the infection (as well as substantial advances in medical and nursing care, including the development of potent antimicrobial chemotherapy, and the establishment of ICU facilities), community-acquired pneumonia (CAP) continues to cause considerable morbidity and mortality worldwide.[1,2] The use of adjunctive therapy, with agents that target diverse or specific

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AFFILIATIONS: From the Division of Pulmonology (Dr Feldman), Department of Internal Medicine, Charlotte Maxeke Johannesburg Academic Hospital and Faculty of Health Sciences, University of the Witwatersrand, Johannesburg; and Institute of Cellular and Molecular Medicine (Dr Anderson), Department of Immunology, Faculty of Health Sciences, University of Pretoria, Pretoria, South Africa.

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CORRESPONDENCE TO: Charles Feldman, MBBCh, DSc, FCCP, Department of Internal Medicine, University of the Witwatersrand Medical School, 7 York Rd, Parktown, 2193, Johannesburg, South Africa; e-mail: charles.feldman@wits.ac.za

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components of disease pathogenesis, represents a potential strategy to improve the poor outcome.[1-4] To this end, various adjunctive therapies have been investigated, many of them proving rather disappointing. One area of reemerging research interest in patients with CAP, first described in 1993,[5] is the occurrence of cardiac complications, which may be the primary cause of treatment failure and are recognized to be associated with worse prognosis.[6,7] This review will describe pathogenic mechanisms in CAP, highlighting aspects that relate to cardiac complications and their mechanisms, as well as identifying potential adjunctive therapies targeting them.

Pathogenesis of CAP

The three most common causes of bacterial CAP are *Streptococcus pneumoniae* (the pneumococcus), *Haemophilus influenzae*, and *Moraxella catarrhalis*. Collectively, these organisms account for > 80% of cases of CAP, the pneumococcus being the predominant cause (> 60% of cases). Colonization of the upper airways by these organisms is mediated via the interaction of bacterial surface adhesins with respiratory epithelium which is a prerequisite for development of invasive disease. During this phase, the organisms coexist with the host, kept in check by host defenses and/or concealment in biofilm.[1]

The transition of these airway colonists to menacing pathogens can be triggered by various events including:

- Genotypic modifications leading to a more virulent phenotype
- Transmission to a suitably vulnerable, immunocompromised host
- Development by the host of an acute or chronic immunosuppressive viral infection.

The CAP pathogens use a range of predominantly protein virulence factors to subvert innate and adaptive pulmonary host defenses, promoting invasion of the lower airways as well as persistence and extrapulmonary dissemination in severe disease.[1]

Containment of the infection until implementation of effective antimicrobial therapy is dependent on the efficacy of innate pulmonary host defenses. Notwithstanding nonspecific airway and infiltrating opsonins, these include various families of pattern recognition receptors present in/on airway cells of the innate immune system (macrophages, dendritic cells, natural killer cells, mast cells), as well as epithelial cells. Well-characterized pattern recognition receptor families which recognize molecular structures common to microbial and viral pathogens include: (1) the Toll-like receptors (TLRs) and nucleotide-binding oligomerization domain (NOD)-like receptors of which there are at least 11 and 22 members, respectively; (2) the inflammasomes, such as NOD-like receptor family, pyrin domain-containing 3 (NLRP3), a subset of nucleotide oligomerization domain-like receptors; and (3) the abundant cytosolic microbial and viral nucleic acid sensors.[8,9]

However, should these mechanisms be overcome by CAP organisms, the resultant sustained and ineffective pulmonary inflammatory response, in concert with bacterial toxins, predisposes to ARDS/acute lung injury. These events in turn also promote extrapulmonary dissemination of the pathogens and their proinflammatory products, leading to a systemic inflammatory response with accompanying endothelial dysfunction and a procoagulant state. The consequences include the potential for the development of acute coronary events, as discussed more fully in the next section, as well as septic shock and multiorgan dysfunction syndrome.[1] A generic scheme summarizing these mechanisms is shown in Figure 1.

CAP, Acute Cardiac Events, and Platelet Activation

With respect to CAP-associated cardiovascular disorders, the increased risk for cardiac events in hospitalized patients may be as high as eightfold in the 15-day period following admission and greatest (100-fold increased risk) within the first 2 to 3 days.[6] Incident cardiac complications associated with increased morbidity and mortality include myocardial infarction (predominantly silent) and new or worsening heart failure or arrhythmias, with the major risk factors being older age, nursing home residence, preexisting chronic respiratory or cardiovascular conditions, severity of CAP, and smoking.[6,7]

In addition to the mechanisms described in the preceding section, a recent study by Cangemi et al[10] has implicated direct effects of CAP pathogens on platelet activation in the pathogenesis of myocardial infarction, providing insights into potential adjunctive antithrombotic strategies. Although the underlying mechanisms of platelet activation in CAP and a causative link with cardiovascular disease and cerebrovascular disease remain to be conclusively established, several possibilities exist, specifically in relation to bacterial CAP. These include the following:

- Direct interaction of bacteria with TLRs expressed in/on platelets, specifically TLR2 and TLR4, which recognize gram-positive cell-wall lipoteichoic