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Community-Acquired Pneumonia

Pathogenesis of Acute Cardiac Events and Potential Adjunctive Therapies

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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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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

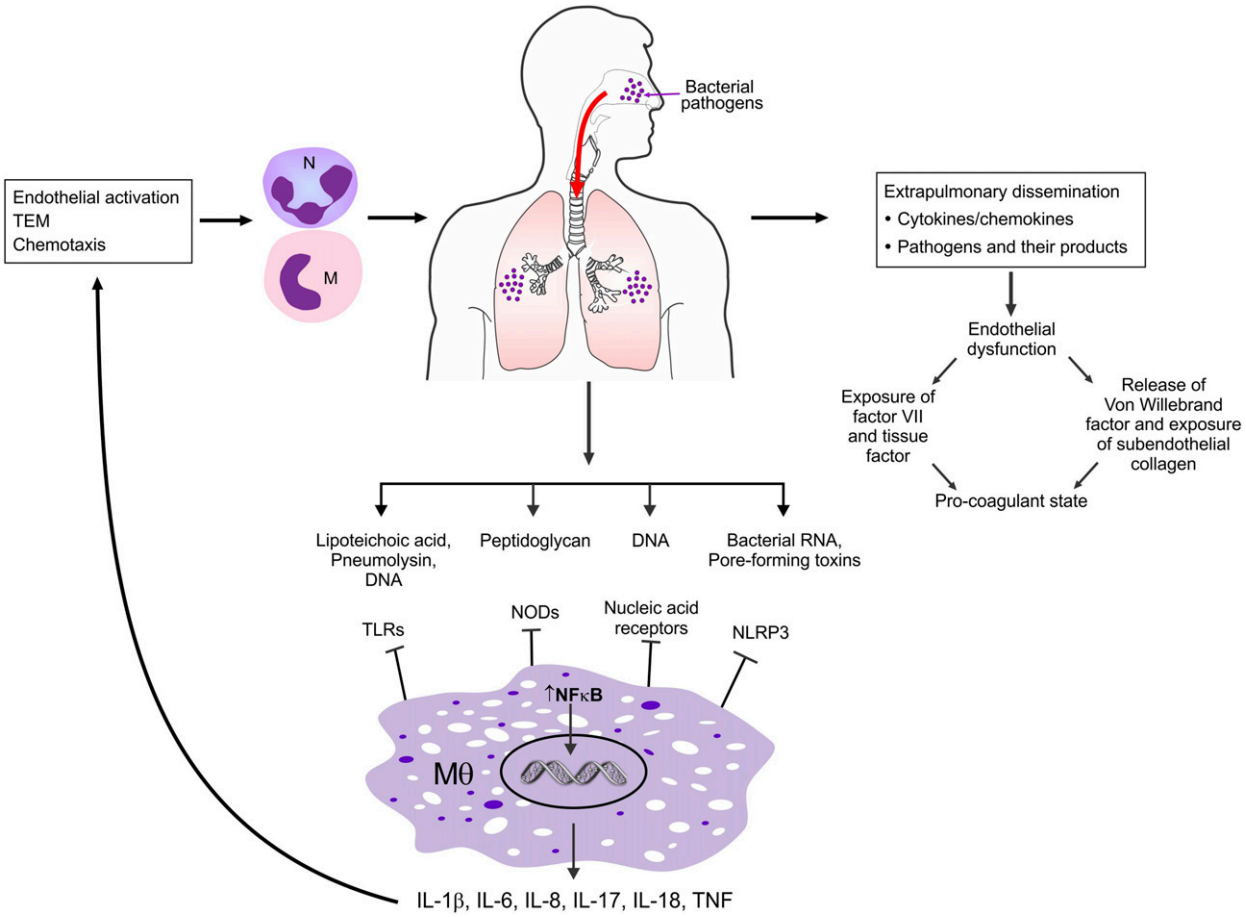

Figure 1 – *The pathogenesis of bacterial community-acquired pneumonia (CAP). The transition of CAP pathogens (purple circles in nasal passage and lungs) from quiescent colonists to an aggressive phenotype enables invasion of the lower airways. Interaction of bacterial cell-wall and intracellular components (lipoteichoic acid, peptidoglycan, nucleic acids, pneumolysin, and other pore-forming toxins) with pattern recognition receptors (T) in/on resident cells of the pulmonary innate immune system (in this case, macrophages) leads to activation of latent cytosolic transcription factors including, but not limited to, NF-κB. Nuclear translocation of the activated transcription factors results in the induction of genes encoding various proinflammatory cytokines/chemokines (IL-1β, IL-6, IL-8, IL-17, IL-18, TNF). These, in turn, promote localized activation of vascular endothelium and presentation of chemoattractants enabling the TEM of monocytes and neutrophils, as well as exudation of proinflammatory complement proteins and acute-phase reactants. Recruitment of these mobilizable, systemic elements of the innate immune system reinforces pulmonary host defenses. However, prolonged and misdirected inflammatory responses may intensify pulmonary damage via the excessive release of indiscriminate phagocyte-derived reactive oxygen species and proteases acting in tandem with microbial cytotoxins; these mechanisms may also favor the extrapulmonary dissemination of CAP pathogens and proinflammatory cytokines/chemokines resulting in a systemic inflammatory response with accompanying endothelial dysfunction and resultant exposure/release of factor VII, tissue factor, von Willebrand factor, and subendothelial collagen, creating a procoagulant state. M = monocyte; Mθ = macrophage; N = neutrophil; NF-κB = nuclear factor κB; NLRP3 = nucleotide-binding oligomerization domain-like receptor family, pyrin domain-containing 3; NOD = nucleotide-binding oligomerization domain; TEM = transendothelial migration; TLR = Toll-like receptor; TNF = tumor necrosis factor.*

acid/peptidoglycan[11] and gram-negative endotoxin, respectively.[12] The consequence is activation of the fibrinogen-binding integrin, glycoprotein IIb/IIIa (GPIIb/IIIa) (αIIbβ3), mobilization of α- and dense granules, and release of adenosine diphosphate (ADP) and production of thromboxane A2 (TxA_2), both potent autocrine and paracrine activators of platelets via their interaction with thromboxane (TP) receptors, respectively, both types being G-protein-coupled receptors (GPCRs). The consequence is platelet aggregation and vasoconstriction.

- Amplification of platelet activation by several strains of bacteria belonging to the *Staphylococcus* and *Streptococcus* genera may also result from their interaction with the platelet α-granule protein, platelet factor-4 (PF4, CXCL4), a prothrombotic, CXC chemokine which also possesses antibacterial activity.[13,14] Pathogen-bound PF4 is recognized by circulating IgG, forming a complex which binds to the platelet FcγRIIA receptor, potentiating GPIIb/IIIa activation by mechanisms which remain to be fully characterized, but appear to involve Src and Syk tyrosine kinases.[13]
- In rodent and murine models of experimental infection, sustained infection with the pneumococcus has been found to trigger atherogenesis and worsen cerebral

ischemia via an IL-1/GPIbα-dependent mechanism, probably due to inflammasome activation, resulting in platelet activation and microvascular coagulation.[15]

Additional mechanisms which may contribute to CAP-associated myocardial infarction include the heterotypic interactions of platelets with neutrophils and vascular endothelium. Activated platelets form stable clusters around neutrophils, a phenomenon known as "satellitism," involving multiple proadhesive mechanisms.[16] These include interactions of P-selectin, CD40 ligand (CD40L), intercellular adhesion molecule-2 (ICAM-2), and GPIbα on platelets with their respective ligands on neutrophils (P-selectin GP ligand-1, CD40, and the β_2-integrins CD11a/CD18 and CD11b/CD18).[17,18] These interactions not only promote adhesion of neutrophils to activated vascular endothelium and transendothelial migration, but also sensitize the prooxidative and proinflammatory activities of these cells, predisposing to endothelial damage and dysfunction, potentially exacerbating microvascular coagulation. In addition, the presentation by activated platelets of the DNA-binding cytokine, high mobility group box 1 protein (HMGB1) to neutrophils has been reported to promote the formation of neutrophil extracellular traps,[19] leading to further endothelial dysfunction due to histone-mediated damage[20] and thrombin generation.[21] These mechanisms of pathogen-associated platelet activation are shown in Figure 2.

Alternative Mechanisms of CAP-Associated Cardiac Events

Experimental studies in mice and macaques have revealed that invasive pneumococcal disease leads to translocation of the pneumococcus into the myocardium resulting in the formation of "unique microlesions that disrupt cardiac function."[22] Bacterial translocation into the heart and formation of microlesions was found to be dependent on the pneumococcal adhesin, choline-binding protein A, and the cholesterol-binding pore-forming cytotoxin, pneumolysin, respectively.[22] In this context, it is noteworthy that statin therapy of severe pneumococcal infection in a murine model of sickle cell disease was found to confer protection against the cytolytic actions of pneumolysin by apparent interference with toxin/membrane cholesterol interactions.[23]

Therapeutic Implications

Among the myriad of adjunctive therapies that have been studied, the three major options are the macrolides, corticosteroids, and statins, all of which have been documented to possess antiinflammatory activities, targeting various cell types and their mediators and, to a greater or lesser extent, to have antiplatelet effects.

Macrolides

The majority of the publications describing patient outcome with the use of macrolide-based antibiotic regimens have documented clinical benefit in patients with CAP, particularly in the more severely ill cases.[24,25] Macrolides have been documented not only to possess adjunctive antiinflammatory, immunomodulatory activity in vitro, but also to inhibit platelet-activating factor (PAF)-mediated platelet aggregation.[26] Although these activities may underpin the benefits of these agents in the management of CAP, differentiating them from antimicrobial activity in the clinical setting is very difficult.[7]

Corticosteroids

The evidence for corticosteroid adjunctive therapy has been less clear cut, although meta-analyses and studies have shown benefit, particularly in the severe CAP subgroup, and especially in the presence of septic shock or with prolonged use of these agents.[27-30] Two randomized placebo-controlled studies have recently been reported.[31,32] The former study among hospitalized adults with CAP documented a shorter time to clinical stability in patients receiving adjunctive prednisone for 7 days.[31] The latter study among patients with severe CAP and high initial inflammatory response (C-reactive protein $>$ 150 mg/L) documented less treatment failure with the use of adjunctive methylprednisolone therapy for 5 days.[32] Another recent study, confirming several earlier reports of the use of prednisolone or methylprednisolone in children with complicated *Mycoplasma pneumoniae* pneumonia, documented rapid defervescence of infection in most children (86 of 90 cases) receiving one of these agents as adjunctive therapy.[33] Interestingly, prednisolone, which appears to be the most effective corticosteroid in the adjunctive therapy of CAP, has been reported to inhibit platelet activation in vitro by a nongenomic mechanism not shared with other types of corticosteroid.[34]

Notwithstanding the fact that some patients who develop CAP may be taking long-term corticosteroids (eg, inhaled corticosteroids) or macrolides, the studies evaluating the use of these agents as adjunctive therapy in CAP have been done with the use of these agents as acute therapies.

Statins

The statins are lipid-lowering drugs used primarily for the prevention and treatment of cardiac conditions.[35] They have a variety of well-characterized pleiotropic

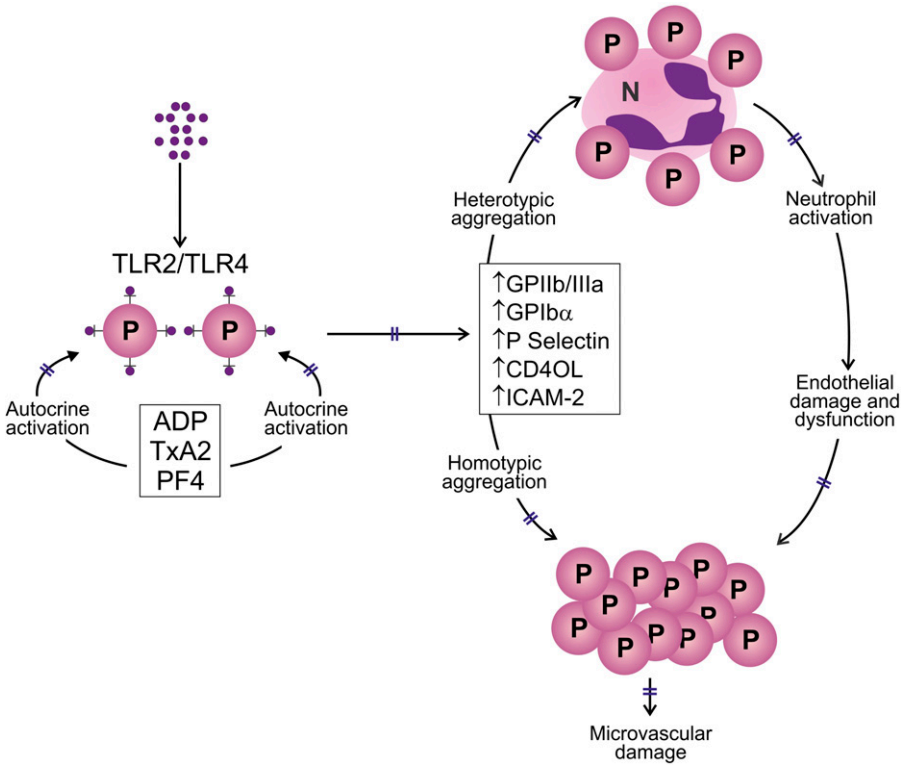

Figure 2 – *Proposed mechanisms of platelet activation in bacterial CAP. The interaction of bacterial pathogens (purple circles) or their liberated cell-wall components with TLRs 2 and 4 (represented by symbol T) on platelets results in platelet activation. This, in turn, is characterized by generation of TxA2 and mobilization of platelet intracellular granules resulting in release of stored ADP. TxA_2 and ADP intensify platelet activation via their respective interactions with thromboxane TP and purinergic P2Y12 receptors. PF4, released via mobilization of intracellular granules, also contributes to platelet activation. This involves interaction of PF4 with CAP pathogens followed by binding of IgG to form a complex, which binds to the platelet FcγRIIA receptor, resulting in activation of the platelet integrin, GPIIb/IIIa (αIIbβ3). In addition to activation of GPIIb/IIIa, these various mechanisms of platelet activation also result in upregulated expression/activation of various other platelet adhesion molecules (GPIbα, P selectin, CD4OL, ICAM-2) which promote homotypic and/or heterotypic platelet aggregation. In the case of the former, homotypic aggregation results in platelet plug formation. With respect to heterotypic aggregation, the binding of platelets to neutrophils intensifies neutrophil activation, causing binding to and damage of vascular endothelium, thereby potentiating platelet activation and thrombus formation via exposure of, and contact with, subendothelial connective tissue. The inhibitory actions of statins on these processes are denoted by the intersecting double lines (=). ADP = adenosine diphosphate; CD4OL = CD40 ligand; GP = glycoprotein; ICAM = intercellular adhesion molecule; P = platelet; PF4 = platelet factor-4; TLR = Toll-like receptor; TP = thromboxane; TxA2 = thromboxane A_2. See Figure 1 legend for expansion of other abbreviations.*

effects, including antiinflammatory and immunomodulatory activities that may contribute to their effectiveness against cardiac disease.[35,36] Many of these target various components of the pathways involved in the pathogenesis of CAP, including the cardiac complications.[36,37]

These pleiotropic effects of statins occur primarily as a consequence of inhibition of activity of the enzyme, 3-hydroxy-3-methyl-glutaryl CoA reductase, not only decreasing the synthesis of mevalonic acid and cholesterol but also of isoprenoids. This latter activity attenuates intracellular signaling mediated via the $G_{\beta\gamma}$ subunit of GPCRs via interference with isoprenylation of the Rac/Rho/Ras family of small GTP-binding proteins. Antiinflammatory activities of statins mediated via interference with isoprenylation include inhibition of the proinflammatory transcription factor, nuclear factor κB (NF-κB),[38] and induction of transcription of the gene encoding the antioxidative enzyme, heme-oxygenase-1.[39]

In addition, statins, via their cholesterol-lowering activity, have been reported to disrupt cholesterol-rich membrane lipid rafts with resultant impairment of intracellular signaling by other types of GPCR such as Gαi[40] as well as the lectin-like oxidized low-density lipoprotein-1 receptor (LOX-1),[41] which are dependent on intact lipid rafts.

Statins, in addition to inhibitory effects on immune and inflammatory cells, have also been reported to suppress platelet activation by various mechanisms, which also appear to be largely attributable to inhibition of HMB-CoA reductase. The most well characterized of these include:

- Decreasing the concentrations of proatherogenic oxLDL-C,[42] an inflammatory mediator which promotes

platelet activation via interactions with the scavenger receptors LOX-1 and CD36, both of which are expressed on platelets,[43,44] and possibly by decreasing scavenger receptor function (LOX-1) and expression (CD36)

- Several mechanisms which suppress platelet activation/aggregation independently of cholesterol-lowering activity, specifically: (1) increased production of the enzyme endothelial nitric oxide synthase by platelets; (2) inhibition of synthesis of TxA_2 secondary to decreased activity of phospholipase A_2; and (3) decreased expression of proadhesive CD40L.[42]

Table 1 summarizes the documented antiplatelet activities of statins, together with those of macrolides, corticosteroids, and selective platelet-targeted agents, few of which have been evaluated in CAP.[26,33,42,45-50] We are unaware of any clinically available selective PAF receptor antagonists. Although the activation of proteinase-activated receptor 1 (thrombin activated), TxA_2 receptors (TP), and the purinergic receptor P2Y12 (ADP activated) is largely independent of isoprenylation, the requirement for cholesterol-rich membrane lipid rafts for optimal activity[41] is consistent with possible modulation of these receptors by statins.

Clinical Studies of Statin Use in Patients With CAP

With respect to clinical relevance, a systematic review evaluated the immunomodulatory effects seen with statin use in patients with CAP. Overall, 17 experimental studies and 17 clinical studies were included in the analysis.[35] In the experimental setting, the findings were as follows: (1) a reduction in release of proinflammatory chemokines and cytokines in patients with CAP, in both the pulmonary and systemic compartments; (2) a reduction in activation and recruitment of neutrophils to the lungs after injury to the lungs; and (3) protection of the host from lung injury associated with the lower respiratory tract infection by attenuation of disruption of the pulmonary vasculature.[35] Evaluation of the clinical studies indicated the following: (1) a decreased risk of pneumonia in individuals on statins was documented in most studies and (2) current statin use was mostly associated with improved survival of pneumonia.

It is important to note, however, that most clinical studies with statins were done in the situation in which patients were currently taking these agents for their lipid-lowering and cardiovascular effects and their risk of acquiring CAP, and the effects of statin use on outcome, once CAP occurred, were compared with matched patients not taking statins. One exception appears to be a study in which the impact of statin administration on days 1 and 2 of hospital admission to patients with pneumonia resulted in a modest benefit on mortality in cases not admitted to the ICU.[51] These findings are consistent with a rapid onset of cardioprotective and antiinflammatory action of statins, as reviewed previously.[52] However, a second randomized, placebo-controlled study of statin administration to hospitalized patients with CAP failed to document either a clinical benefit or a reduction in inflammatory cytokines at 48 h.[53]

With respect to case control and cohort studies, these have documented that current statin use was associated with a decreased risk of hospitalization for pneumonia and lower 30-day mortality,[54] as well as lower mortality during the 6-month period following pneumonia.[55] A retrospective cohort study documented that statin use was associated with decreased mortality in patients with pneumococcal pneumonia on days 7, 14, 20, and 30.[56] Interestingly, in the latter study, mortality was not decreased in patients given a macrolide for therapy, nor in those on a macrolide as well as a statin compared with those not on a macrolide. One retrospective observational cohort study documented that patients who received a statin on day 1 or day 2 of hospital admission for pneumonia had a moderate reduction in mortality among cases not admitted to the ICU.[51]

Three additional systematic reviews and meta-analyses have been published interrogating the potential benefit of statins in the prevention and/or mortality of CAP.[57-59] While all showed benefit in one or more of the end points, all three indicated the need for caution in the interpretation of the data due to a number of reasons, including low quality of evidence (observational study designs, heterogeneity, publication bias), weakening of the association in important subgroups accounting for patient differences (eg, severity of illness, smoking, and vaccination status) and in studies with greater methodologic rigor, and substantial statistical and clinical heterogeneity.[57-59] Another consideration is the potential confounding that may be associated with the so-called "healthy user effect," which suggests that statin users may be more health conscious than nonusers and the clinical benefits seen may relate to a healthier lifestyle and greater compliance with both statin use and other preventative health measures rather than to the use of statins per se.[35]

Antiplatelet Agents

There is a paucity of definitive studies documenting the potential benefits of antiplatelet agents on CAP outcomes.[3] In the recent study by Cangemi et al,[10]

TABLE 1] Pharmacologic Agents That Suppress Platelet Activation, Most of Which Have Not Been Evaluated in the Clinical Setting of CAP

Agent	Cellular Target	Status	Study
Statins	• LOX-1/CD36 antagonism • Decreased expression of CD40L • NF-κB inhibition • PLA_2 inhibition • eNOS enhancement • Heme-oxygenase induction	Available clinically	Tong and Tergaonkar,[38] Mrad et al,[39] Quinton et al,[40] Matarazzo et al,[41] Owens and Mackman,[42] Marwali et al,[43] Podrez et al[44]
Aspirin	Cyclooxygenase-1 inhibition NF-κB inhibition	Available clinically	Fontana et al,[45] Weber et al,[46] Akinosoglou and Alexopoulos[48]
Vorapaxar	PAR-1 antagonism	Available clinically	Gurbel et al[47]
Clopidogrel, prasugrel, ticagrelor	P2Y12 receptor antagonism	Available clinically	Akinosoglou and Alexopoulos,[48] Ferri et al[49]
Eptifibatide, tirofiban	GPIIb/IIIa antagonism	Available clinically	Akinosoglou and Alexopoulos[48]
Ozagrel	TS inhibition	Limited availability; registered in Japan for asthma and stroke, as well as in China and South Korea	Fontana et al[45]
Ramatroban, seratrodast	TP receptor antagonism	Limited availability; registered in Japan for asthma and rhinitis, as well as in China	Fontana et al[45]
Picotamide/EV-077	Dual TS/TP receptor inhibition/antagonism	Picotamide is registered in Italy for peripheral vascular disease; EV-077 is in the advanced clinical trial stages of development for the treatment of vascular inflammation in diabetes mellitus and coronary artery disease	Fontana et al[45]
Prednisolone	Unknown, but believed to be nongenomic	Preclinical studies	Liverani et al[34]
Azithromycin, clarithromycin	PAF antagonism?	Preclinical studies	Tsoupras et al[26]
Fucosylated chondroitin sulfates	Adhesion molecule (L-/P-selectin) antagonism	Preclinical studies	Panagos et al[50]

CAP = community-acquired pneumonia; CD40L = CD40 ligand; eNOS = endothelial nitric oxide synthase; GP = glycoprotein; LOX = lectin-like oxidized low-density lipoprotein-1 receptor; NF-κB = nuclear factor κB; PAF = platelet-activating factor; PAR-1 = proteinase-activated receptor 1; PLA_2 = phospholipase A_2; TP = thromboxane; TS = thromboxane synthase.

administration of aspirin at a dose of 100 mg/d had no effect on either platelet activation or the occurrence of cardiovascular events in patients with pneumonia. These authors suggest that the dose of aspirin they used may have been inadequate and propose that additional dose-ranging studies be undertaken. A single study of patients on prior clopidogrel therapy showed trends toward both an increased incidence of CAP, as well as a decrease in its severity, without controlling for aspirin use.[60]

An integrated scheme of the likely sites of the therapeutic activities of statins and the other adjunctive therapies, as well as those of the selective antiplatelet agents listed in Table 1, is shown in Figure 3.

Conclusions

Despite all advances in medical care, patients with CAP still have considerable morbidity and mortality. It has been suggested that adjunctive therapy, with the addition of agents that target aspects of disease pathogenesis may

be helpful in improving outcome and to this end a number of agents have been considered. Recent research indicating the relatively frequent occurrence of cardiac events in patients with CAP, which has been documented to be associated with a poorer prognosis, has heightened interest in the use of adjunctive therapies targeting this aspect of the disease pathogenesis. Notwithstanding the potential role of macrolides and corticosteroids, the most promising agents targeting these cardiac events are statins and selective inhibitors of platelet activation. Most of the studies with statins are, however, confounded by multiple methodologic and statistical flaws, compounded by the possibility of a "healthy user effect." Other aspects of statin use, as potential adjunctive therapy in CAP, that need clarification include identification of those statins with the best therapeutic efficacy, their role as an acute intervention in the setting of CAP, the optimal dose that is required, and the optimal duration of treatment to achieve these effects. While similar considerations also apply to all of the other adjunctive therapies described, there is a particular dearth of information regarding the selective antiplatelet agents with regard to their cardioprotective potential in the setting of CAP. Furthermore, future studies should also focus on combinations of the various adjunctive agents. All of these questions are best answered by well-designed randomized controlled trials.

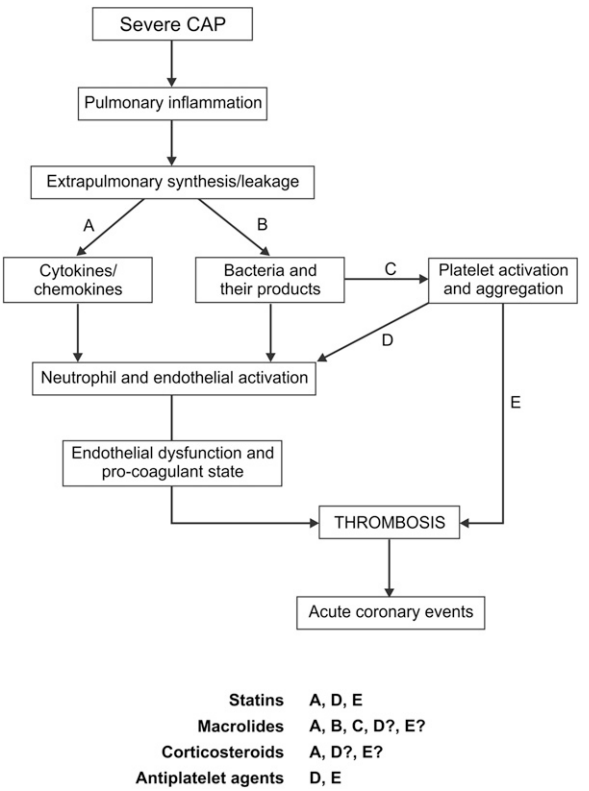

Figure 3 – *Integrated scheme showing the probable sites of the therapeutic activities of statins, macrolides, corticosteroids, and selective antiplatelet agents. This scheme shows the interactions between inflammation, platelet activation, and coagulation during severe CAP, indicating the proposed sites of action of the various adjunctive agents. See Figure 1 legend for expansion of abbreviation.*

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