

Community-acquired pneumonia: Pathogenesis of acute cardiac events and potential adjunctive therapies

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ABSTRACT

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 10-15% in hospitalized cases. CAP, considered by many to be the most under-estimated 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 which may undermine the success of antimicrobial therapy. Adjunctive anti-inflammatory 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 which possess anti-inflammatory and/or platelet-targeted activities. Statins, which not only possess anti-inflammatory activity, but which 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 pharmacological control thereof, with emphasis on statins.

INTRODUCTION

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 intensive care unit 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 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 re-emerging 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 a 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 co-exist 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 utilize 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 extra-pulmonary 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 non-specific airway and infiltrating opsonins, these include various families of pattern recognition receptors (PRRs) 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 PRR families which recognize molecular structures common to

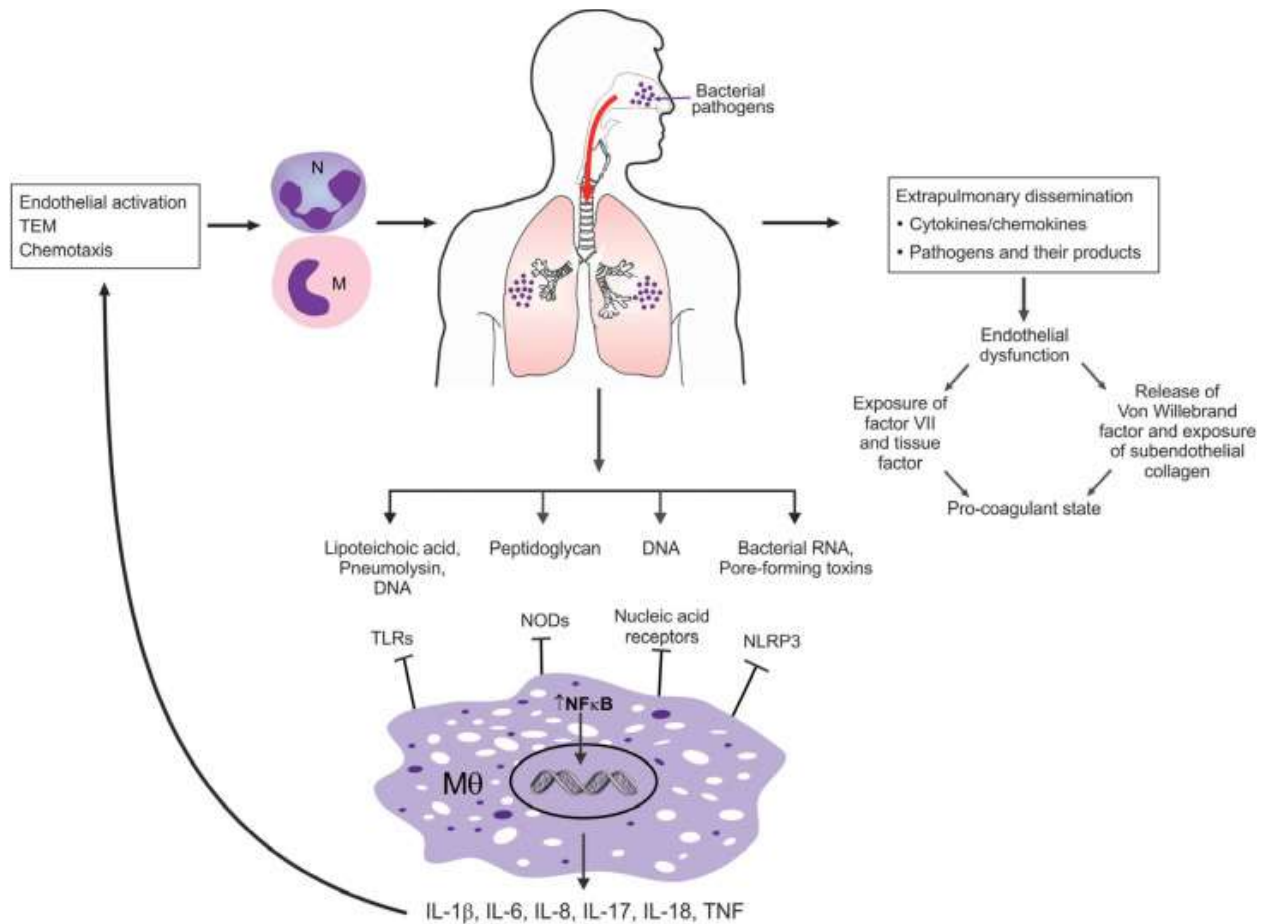


Figure 1: The pathogenesis of bacterial CAP. The transition of CAP pathogens (purple circles in nasal passage and lungs) from quiescent colonists to an aggressive phenotype enables invasion of the lower airways. Interaction of bacterial cell-wall and intracellular components (lipoteichoic acid, peptidoglycan, 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, indicated by Mθ) leads to activation of latent cytosolic transcription factors including, but not limited to, nuclear factor kappa B (NFκB). Nuclear translocation of the activated transcription factors results in the induction of genes encoding various pro-inflammatory 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 transendothelial migration (TEM) of monocytes (M) and neutrophils (N), as well as exudation of pro-inflammatory 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 pro-inflammatory 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 sub-endothelial collagen, creating a pro-coagulant state.

microbial and viral pathogens, include : i) the Toll-like receptors (TLRs) and nucleotide oligomerization domain-like receptors (NLRs) of which there are at least 11 and 22 members respectively; ii) the inflammasomes, such as NLPR3, a subset of NLRs; and iii) 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 acute respiratory distress syndrome/ acute lung injury. These events in turn also promote extrapulmonary dissemination of the pathogens and their pro-inflammatory products leading to a systemic inflammatory response with accompanying endothelial dysfunction and a pro-coagulant state. The consequences include the potential for the development of acute coronary events, as discussed more fully below, 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 8-fold in the 15 day period following admission, and greatest (100-fold increased risk) within the first 2 – 3 days.⁶ Incident cardiac complications associated with increased morbidity and mortality include myocardial infarction (MI, predominantly silent) and new or worsening heart failure or arrhythmias, with the major risk factors being older age, nursing home residence, pre-existing chronic respiratory or cardiovascular conditions, severity of CAP, and smoking.^{6,7}

In addition to the mechanisms described above, a recent study by Cangemi et al. has implicated direct effects of CAP pathogens on platelet activation in the pathogenesis of myocardial infarction, providing insights into potential adjunctive anti-thrombotic strategies.¹⁰ Although the underlying mechanisms of platelet activation in

CAP and a causative link with CVD and cerebrovascular disease remain to be conclusively established, several possibilities exist, specifically in relation to bacterial CAP. These include:

- direct interaction of bacteria with TLRs expressed in/on platelets, specifically TLR2 and TLR4 which recognize Gram-positive cell-wall lipoteichoic acid/peptidoglycan¹¹ and Gram-negative endotoxin respectively.¹² The consequence is activation of the fibrinogen-binding integrin, GPIIb/IIIa (α IIb β 3), mobilization of α - and dense granules, and release of adenosine diphosphate (ADP) and production of thromboxane A₂ (TxA₂), both potent autocrine and paracrine activators of platelets via their interaction with P2Y₁₂ purinergic and TxA₂ (TP) receptors respectively, both types being G-protein-coupled receptors (GPCR). 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 pro-thrombotic, CXC chemokine which also possesses antibacterial activity.^{13,14} Pathogen-bound PF4 is recognized by circulating immunoglobulin G, forming a complex which binds to the platelet Fc γ RIIA 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 interleukin (IL)-1/glycoprotein (GP)Ib α -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

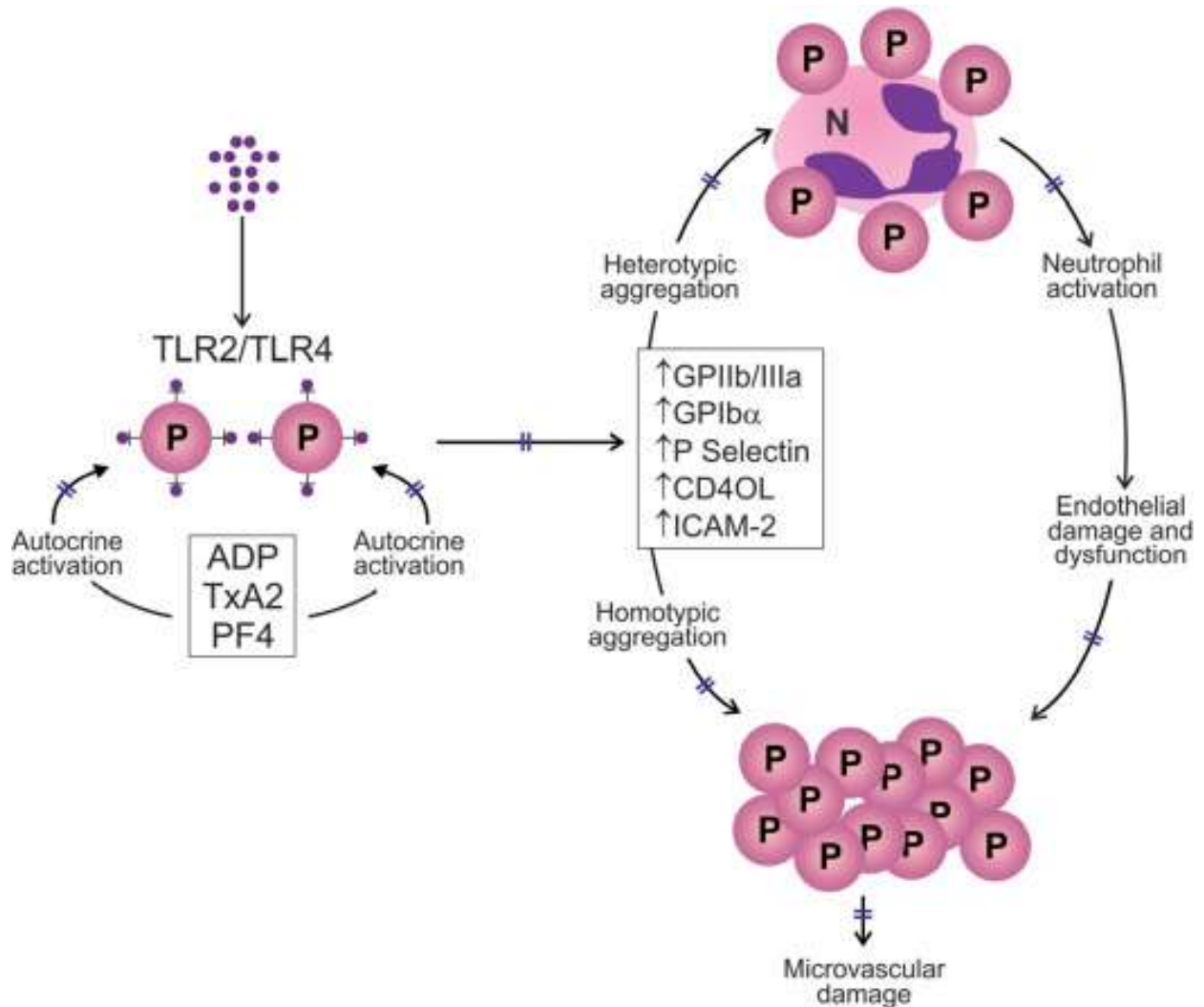


Figure 2: Proposed mechanisms of platelet activation in bacterial CAP. The interaction of bacterial pathogens (purple circles) or their liberated cell-wall components with Toll-like receptors (TLRs) 2 and 4 (represented by symbol T) on platelets (P) results in platelet activation. This, in turn, is characterized by generation of thromboxane A₂ (TxA₂) and mobilization of platelet intracellular granules resulting in release of stored adenosine diphosphate (ADP). TxA₂ and ADP intensify platelet activation via their respective interactions with thromboxane TP and purinergic P2Y₁₂ receptors. Platelet factor-4 (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 (alpha IIb beta 3). 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, CD40L, 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 sub-endothelial connective tissue. The inhibitory actions of statins on these processes are denoted by the intersecting double lines (=).

endothelium. Activated platelets form stable clusters around neutrophils, a phenomenon known as “satellitism,” involving multiple pro-adhesive mechanisms.¹⁶ These include interactions of P-selectin, CD40L, intercellular adhesion molecule-2 (ICAM-2) and GPIIb α 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 trans-endothelial migration, but also sensitize the pro-oxidative and pro-inflammatory 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 damage²⁰ 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 were found to be dependent on the pneumococcal adhesin, choline-binding protein A (CbpA) 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 anti-inflammatory 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 anti-inflammatory, 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 recent 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 > 150mg/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 (86/90 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 non-genomic mechanism not shared with other types of corticosteroid.³⁴

Notwithstanding the fact that some patients who develop CAP may be taking long-term corticosteroids (e.g. 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 effects, including anti-inflammatory 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 (HMG) 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_{βγ} subunit of GPCRs via interference with isoprenylation of the Rac/Rho/Ras family of small GTP-binding proteins. Anti-inflammatory activities of statins mediated via interference with isoprenylation include inhibition of the pro-inflammatory transcription factor, nuclear factor kappa B (NFκB).³⁸ and induction of transcription of the gene encoding the anti-oxidative 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 Gai,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-C⁴² 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: i) increased production of the enzyme endothelial nitric oxide synthase (eNOS) by platelets; ii) inhibition of synthesis of TxA₂ secondary to decreased activity of phospholipase A₂; and iii) decreased expression of pro-adhesive 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 (PAR1, thrombin activated), TxA₂ receptors (TP) and the purinergic receptor, P2Y₁₂ (ADP activated) is largely independent of isoprenylation, the requirement for cholesterol-rich membrane lipid rafts for optimal activity⁴¹ 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 recent 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

Table 1: Pharmacological agents which suppress platelet activation most of which have not been evaluated in the clinical setting of CAP

| <u>Agent</u> | <u>Cellular target</u> | <u>Status</u> | <u>Ref</u> |
|------------------------------------|---|---|------------|
| Statins | <ul style="list-style-type: none"> • LOX-1/CD36 antagonism • Decreased expression of CD40L • NFκB inhibition • PLA₂ inhibition • eNOS enhancement • heme-oxygenase induction | Available clinically | 38-44 |
| Aspirin | Cyclooxygenase-1 inhibition NFκB inhibition | Available clinically | 45,46,48 |
| Vorapaxar | PAR-1 antagonism | Available clinically | 47 |
| Clopidogrel, prasugrel, ticagrelor | P2Y12 receptor antagonism | Available clinically | 48,49 |
| Eptifibatide, tirofiban | GPIIb/IIIa antagonism | Available clinically | 48 |
| Ozagrel | Thromboxane synthase (TS) inhibition | Limited availability; registered in Japan for asthma and stroke, as well as in China and South Korea | 45 |
| Ramatroban, Seretrodast | TP receptor antagonism | Limited availability; registered in Japan for asthma and rhinitis, as well as in China | 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 | 45 |
| Prednisolone | Unknown, but believed to be non-genomic | Pre-clinical studies | 34 |
| Azithromycin, clarithromycin | PAF antagonism? | Pre-clinical studies | 26 |
| Fucosylated chondroitin sulfates | Adhesion molecule (L/P-selectin) antagonism | Pre-clinical studies | 50 |

experimental setting the findings were as follows: i) a reduction in release of pro-inflammatory chemokines and cytokines in patients with CAP, in both the pulmonary and systemic compartments; ii) a reduction in activation and recruitment of neutrophils to the lungs after injury to the lungs; and iii) 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: i) a decreased risk of pneumonia in individuals on statins was documented in most studies; and ii) 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 to matched patients not taking statins. One exception appears to be a study in which the impact of statin administration on day 1 and 2 of hospital admission to patients with pneumonia resulted in a modest benefit on mortality in cases not admitted to the intensive care unit.⁵¹ These findings are consistent with a rapid onset of cardioprotective and anti-inflammatory 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 hours.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

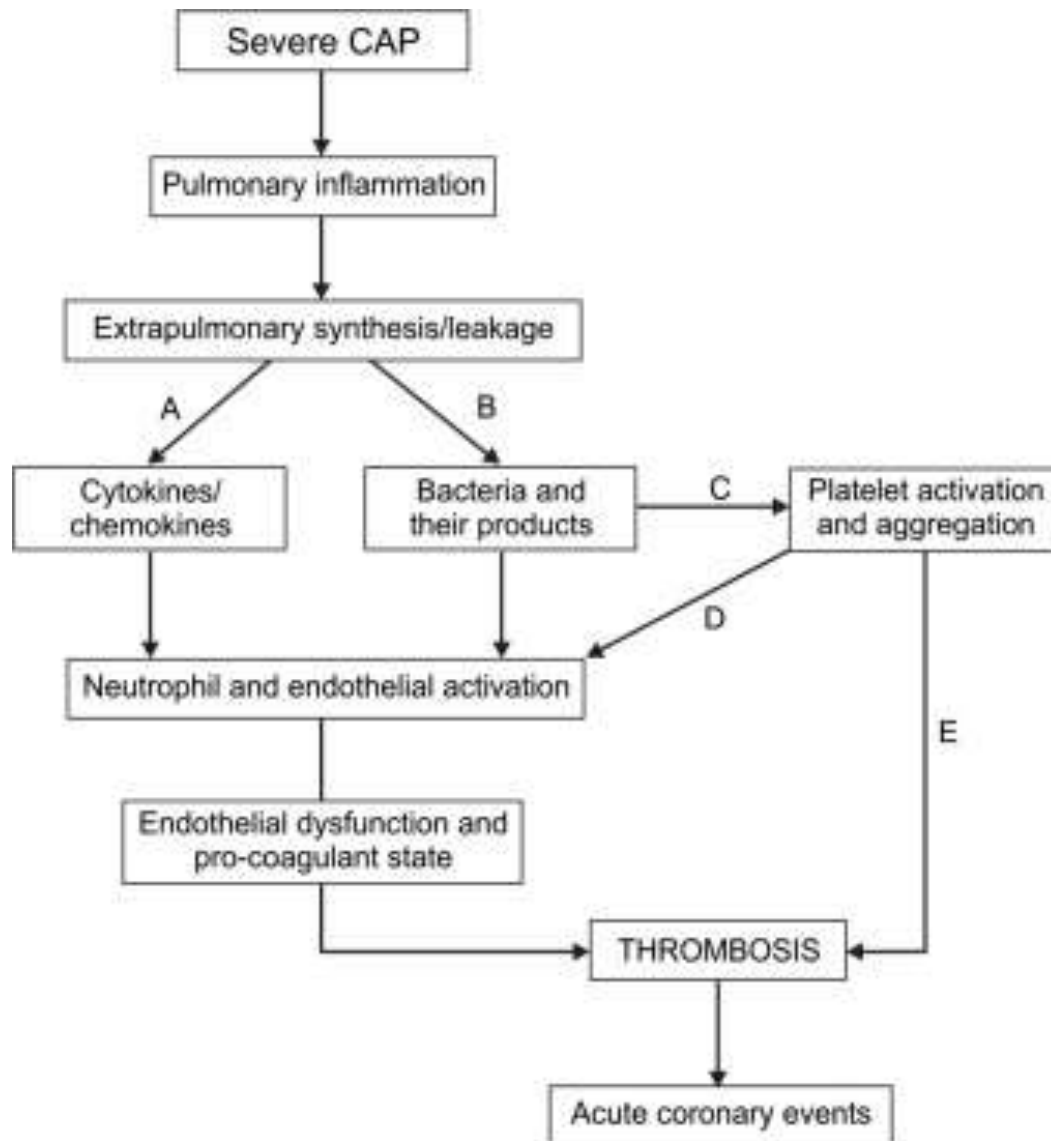
for pneumonia had a moderate reduction in mortality among cases not admitted to the intensive care unit.⁵⁷

Three additional systematic reviews and meta-analyses have been published recently interrogating the potential benefit of statins in the prevention and/or mortality of CAP.⁵⁸⁻⁶⁰ While all showed benefit in one or more of the endpoints, 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 (e.g. severity of illness, smoking and vaccination status) and in studies with greater methodological rigor, and substantial statistical and clinical heterogeneity.⁵⁸⁻⁶⁰ 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 non-users 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

Anti-platelet agents

There is a paucity of definitive studies documenting the potential benefits of anti-platelet agents on CAP outcomes.⁶¹ In the recent study by Cangemi et al. mentioned above, administration of aspirin at a dose of 100mg per day had no effect on either platelet activation or the occurrence of cardiovascular events in patients with pneumonia.¹⁰ 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 towards both an increased incidence of CAP, as well as a decrease in its severity, without controlling for aspirin use.⁶²

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.



| | |
|----------------------------|------------------------|
| Statins | A, D, E |
| Macrolides | A, B, C, D?, E? |
| Corticosteroids | A, D?, E? |
| Antiplatelet agents | D, E |

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.

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, that 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 methodological 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 anti-platelet 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 these questions are best answered by well-designed randomized controlled trials.

REFERENCES

1. Steel HC, Cockeran R, Anderson R, et al. Overview of community-acquired pneumonia and the role of inflammatory mechanisms in the immunopathogenesis of severe pneumococcal disease. *Mediators Inflamm* 2013; 2013:490346

2. Musher DM, Thorner AR. Community-acquired pneumonia. *N Engl J Med* 2014; 371:1619–1628
3. Corrales-Medina VF, Musher DM. Immunomodulatory agents in the treatment of community-acquired pneumonia: A systematic review. *J Infect* 2011; 63:187–199
4. Faverio P, Restrepo MI. Non-antibiotic therapies for CAP. *Eur Respir Monogr* 2014; 63:219–233
5. Seedat MA, Feldman C, Skoularigis J, et al. A study of acute community-acquired pneumonia, including details of cardiac changes. *Q J Med* 1993; 86:669–675
6. Corrales-Medina VF, Madjid M, Musher DM. Role of acute infection in triggering acute coronary syndromes. *Lancet Infect Dis* 2010;10:83–92
7. Corrales-Medina VF, Musher DM, Wells GA, et al. Cardiac complications in patients with community-acquired pneumonia: incidence, timing, risk factors, and association with short term mortality. *Circulation* 2012; 125:773–781
8. Opitz B, van Laak V, Eitel J, et al. Innate immune recognition in infectious and non-infectious diseases of the lung. *Am J Respir Crit Care Med* 2010; 181:1294–1309
9. Eldridge MJ, Shenoy AR. Antimicrobial inflammasomes: unified signalling against diverse bacterial pathogens. *Curr Opin Microbiol* 2015; 23:32–41
10. Cangemi R, Casciaro M, Rossi E, et al. Platelet activation is associated with myocardial infarction in patients with pneumonia. *J Am Coll Cardiol* 2014; 64:1917–1925
11. Keane C, Tilley D, Cunningham A, et al. Invasive *Streptococcus pneumoniae* trigger platelet activation via Toll-like receptor 2. *J Thromb Haemost* 2010; 8:2757–2765

12. Tamagawa-Mineoka R. Important roles of platelets as immune cells in the skin. *J Dermatol Sci* 2015; 77:93–101
13. Arman M, Krauel K, Tilley DO, et al. Amplification of bacteria-induced platelet activation is triggered by FcγRIIA, integrin αIIbβ3, and platelet factor 4. *Blood* 2014; 123:3166–3174
14. Naik UP. Bacteria exploit platelets. *Blood* 2014; 123:3067–3068
15. Dénes Á, Pradillo JM, Drake C, et al. *Streptococcus pneumoniae* worsens cerebral ischemia via interleukin 1 and platelet glycoprotein Iba. *Ann Neurol* 2014; 75:670–683
16. Page C, Pitchford S. Neutrophil and platelet complexes and their relevance to neutrophil recruitment and activation. *Int Immunopharmacol* 2013; 17:1176–1184
17. Jin R, Yu S, Song Z, et al. Soluble CD40 ligand stimulates CD40-dependent activation of the β2 integrin Mac-1 and protein kinase C zeta (PKCζ) in neutrophils: implications for neutrophil-platelet interactions and neutrophil oxidative burst. *PLoS One* 2013; 8:e64631
18. Li J, Kim K, Hahm E, et al. Neutrophil AKT2 regulates heterotypic cell-cell interactions during vascular inflammation. *J Clin Invest* 2014; 124:1483–1496
19. Maugeri N, Campana L, Gavina M, et al. Activated platelets present high mobility group box 1 to neutrophils, inducing autophagy and promoting the extrusion of neutrophil extracellular traps. *J Thromb Haemost* 2014; 12:2074–2088
20. Saffarzadeh M, Juenemann C, Queisser MA, et al. Neutrophil extracellular traps directly induce epithelial and endothelial cell death: a predominant role of histones. *PLoS One* 2012; 7:e32366

21. Gould TJ, Vu TT, Swystun LL, et al. Neutrophil extracellular traps promote thrombin generation through platelet-dependent and platelet-independent mechanisms. *Arterioscler Thromb Vasc Biol* 2014; 34:1977–1984
22. Brown AO, Mann B, Gao G, et al. *Streptococcus pneumoniae* translocates into the myocardium and forms unique microlesions that disrupt cardiac function. *PLoS Pathog* 2014; 10:e1004383
23. Rosch JW, Boyd AR, Hinojosa E, et al. Statins protect against fulminant pneumococcal infection and cytolysin toxicity in a mouse model of sickle cell disease. *J Clin Invest* 2010; 120:627–635
24. Asadi L, Sligl WI, Eurich DT, et al. Macrolide-based regimens and mortality in hospitalized patients with community-acquired pneumonia: A systematic review and meta-analysis. *Clin Infect Dis* 2012; 55:371–380
25. Sligl WI, Asadi L, Eurich DT, et al. Macrolides and mortality in critically ill patients with community-acquired pneumonia: A systematic review and meta-analysis. *Crit Care Med* 2014; 42:420–432.
26. Tsoupras AB, Chini M, Tsogas N, et al. *In vitro* anti-inflammatory and anti-coagulant effects of antibiotics towards Platelet Activating Factor and thrombin. *J Inflamm* 2011; 8:17
27. Nie W, Zhang Y, Cheng J, et al. Corticosteroids in the treatment of community-acquired pneumonia in adults: A meta-analysis. *PLoS One* 2012; 7:e47926
28. Confalonieri M, Annane D, Antonaglia C, et al. Is prolonged low-dose glucocorticoid treatment beneficial in community-acquired pneumonia? *Curr Infect Dis Rep* 2013; 15:158–166

29. Shafiq M, Mansoor MS, Khan AA, et al. Adjuvant steroid therapy in community-acquired pneumonia: A systematic review and meta-analysis. *Journal of Hospital Medicine* 2013; 8:68–75
30. Cheng M, Pan Z-y, Yang J, et al. Corticosteroid therapy for severe community-acquired pneumonia: A meta-analysis. *Respir Care* 2014; 59:557–563.
31. Blum CA, Nigro N, Briel M, et al. Adjunct prednisone therapy for patients with community-acquired pneumonia: a multicentre, double-blind, randomised, placebo-controlled trial. *Lancet* 2015; [E-pub ahead of print].
32. Torres A, Sibila O, Ferrer M, et al. Effect of corticosteroids on treatment failure among hospitalized patients with severe community-acquired pneumonia and high inflammatory response: a randomized clinical trial. *JAMA* 2015; 313:677–686.
33. Youn YS, Lee SC, Rhim JW, et al. Early additional immune-modulators for *Mycoplasma pneumoniae* pneumonia in children: an observation study. *Infect Chemother* 2014; 46:239–247.
34. Liverani E, Banerjee S, Roberts W, et al. Prednisolone exerts exquisite inhibitory properties on platelet functions. *Biochem Pharmacol* 2012; 83:1364–1373
35. Troeman DPR, Postma DF, van Werkhoven CH, et al. The immunomodulatory effects of statins in community-acquired pneumonia: A systematic review. *J Infect* 2013; 67:93–101
36. Terblanche M, Almog Y, Rosenson RS, et al. Statins and sepsis: multiple modifications at multiple levels. *Lancet* 2007; 7:358–368

37. Van der Meij E, Koning GG, Vriens PW, et al. A clinical evaluation of statin pleiotropy: statins selectively and dose-dependently reduce vascular inflammation. *PLoS One* 2013; 8:e53882
38. Tong L, Tergaonkar V. Rho protein GTPases and their interactions with NF κ B: crossroads of inflammation and matrix biology. *Biosci Rep* 2014; 34:e00115
39. Mrad MF, Mouawad CA, Al-Hariri M, et al. Statins modulate transcriptional activity of heme-oxygenase-1 promoter in NIH 3T3 cells. *J Cell Biochem* 2012; 113:3466–3475
40. Quinton TM, Kim S, Jin J, et al. Lipid rafts are required in G α_i signaling downstream of the P2Y₁₂ receptor during ADP-mediated platelet activation. *J Thromb Haemost* 2005; 3:1036–1041
41. Matarazzo S, Quitadamo MC, Mango R, et al. Cholesterol-lowering drugs inhibit lectin-like oxidized low-density lipoprotein-1 receptor function by membrane raft disruption. *Mol Pharmacol* 2012; 82:246–254
42. Owens AP 3rd, Mackman N. The antithrombotic effects of statins. *Annu Rev Med* 2014; 65:433–445
43. Marwali MR, Hu CP, Mohandas B, et al. Modulation of ADP-induced platelet activation by aspirin and pravastatin: role of lectin-like oxidized low-density lipoprotein receptor-1, nitric oxide, oxidative stress, and inside-out integrin signaling. *J Pharmacol Exp Ther* 2007; 322:1324–1332
44. Podrez EA, Byzova TV, Febbraio M, et al. Platelet CD36 links hyperlipidemia, oxidant stress and a prothrombotic phenotype. *Nat Med* 2007; 13:1086–1095
45. Fontana P, Zufferey A, Daali Y, et al. Antiplatelet therapy: targeting the TxA₂ pathway. *J Cardiovasc Transl Res* 2014; 7:29–38

46. Weber C, Erl W, Pietsch A, et al. Aspirin inhibits nuclear factor-kappa B mobilization and monocyte adhesion in stimulated human endothelial cells. *Circulation* 1995; 91:1914–1917
47. Gurbel PA, Jeong YH, Tantry US. Vorapaxar: a novel protease-activated receptor-1 inhibitor. *Expert Opin Investig Drugs* 2011; 20:1445–1453
48. Akinosoglou K, Alexopoulos D. Use of antiplatelet agents in sepsis: a glimpse into the future. *Thromb Res* 2014; 133:131–138
49. Ferri N, Corsini A, Bellosta S. Pharmacology of the new P2Y₁₂ receptor inhibitors: insights on pharmacokinetic and pharmacodynamics properties. *Drugs* 2013; 73:1681–1709
50. Panagos CG, Thomson DS, Moss C, et al. Fucosylated chondroitin sulfates from the body wall of the sea cucumber *Holothuria forskali*: conformation, selectin binding, and biological activity. *J Biol Chem* 2014; 289:28284–28298
51. Rothberg MB, Bigelow C, Pekow PS, et al. Association between statins given in hospital and mortality in pneumonia patients. *J Gen Intern Med* 2012; 27:280–286.
52. Fedson DS. Pandemic influenza: a potential role for statins in treatment and prophylaxis. *Clin Infect Dis* 2006; 43:199–205.
53. Viasus D, Garcia-Vidal C, Simonetti AF, et al. The effect of simvastatin on inflammatory cytokines in community-acquired pneumonia: a randomised, double-blind, placebo-controlled trial. *BMJ Open* 2015; 5:e006251.
54. Nielsen AG, Nielsen RB, Riis AH, et al. The impact of statin use on pneumonia risk and outcome: a combined population-based case-control and cohort study. *Critical Care* 2012; 16:R122

55. Douglas I, Evand S, Smeeth L. Effect of statin treatment on short term mortality after pneumonia episode: cohort study. *BMJ* 2011; 342:d1642
56. Doshi SM, Kulkarni PA, Liao JM, et al. The impact of statin and macrolide use on early survival in patients with pneumococcal pneumonia. *Am J Med Sci* 2013; 345:173–177
57. Rothberg MB, Bigelow C, Pekow PS, et al. Association between statins given in hospital and mortality in pneumonia patients. *J Gen Intern Med* 2011; 27:280–286
58. Kwok CS, Yeong J K-Y, Turner RM, et al. Statins and associated risk of pneumonia: a systematic review and meta-analysis of observational studies. *Eur J Clin Pharmacol* 2012; 68:747–755
59. Chopra V, Rogers MAM, Buist M, et al. Is statin use associated with reduced mortality after pneumonia: A systematic review and meta-analysis. *Am J Med* 2012; 125:1111–1123
60. Khan AR, Riaz M, Abdulhak AAB, et al. The role of statins in prevention and treatment of community-acquired pneumonia: A systematic review and meta-analysis. *PLoS One* 2013; 8:e52929.
61. Corrales-Medina VF, Musher DM. Immunomodulatory agents in the treatment of community-acquired pneumonia: a systematic review. *J Infect* 2011; 63:187–199.
62. Gross AK, Dunn SP, Feola DJ, et al. Clopidogrel treatment on the incidence and severity of community acquired pneumonia in a cohort study and meta-analysis of antiplatelet therapy in pneumonia and critical illness. *J Thromb Thrombolysis* 2013; 35:147–154.