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Pneumonia as a cardiovascular disease

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ABSTRACT

Community-acquired pneumonia (CAP) is an important cause of death around the globe. Up to 30% of patients admitted to hospital for CAP develop cardiovascular complications (i.e. new/worsening heart failure, new/-worsening arrhythmias, myocardial infarctions and/or strokes), acutely and up to 10 years thereafter. Cardiac complications result from complex interactions between preexisting conditions, relative ischaemia, upregulation of the sympathetic system, systemic inflammation and direct pathogen-mediated damage to the cardiovascular system. The exact mechanisms underlying the direct host–pathogen interactions are of great interest to identify potential therapeutic and preventative targets for CAP. In this review, we summarize the epidemiological data, risk factors and the pathogen-driven cardiovascular damage affecting patients with CAP.

Key words: arrhythmias, heart failure, myocardial infarction, pneumonia.

Abbreviations: ACE, angiotensin-converting enzyme; ACS, acute coronary syndrome; ARB, angiotensin receptor blocker; CAP, community-acquired pneumonia; CC, cardiovascular complication; CRP, C-reactive protein; CVD, cardiovascular disease; IPD, invasive pneumococcal disease; MI, myocardial infarction; NHP, non-human primates; PAR, protease-activated receptor; Ply, pneumolysin; RR, risk ratio; sP-selectin, soluble P-selectin; SRMA, systematic review and meta-analysis.

Glossary: ST segment, The ST segment is the flat, isoelectric section of the electrocardiogram (ECG) between the end of the S wave (the J point) and the beginning of the T wave

INTRODUCTION

Pneumonia and cardiovascular diseases (CVD) are leading causes of morbidity and mortality worldwide.[1] Community-acquired pneumonia (CAP) is estimated to affect 5–6 million people in the United States annually, leading to 1.1 million hospital admissions and 60 000 deaths.[2,3] More than half of the elderly patients who present to hospital with CAP have preexisting chronic cardiac conditions.[4] Acute infections such as CAP can affect the cardiovascular system by multiple mechanisms and directly cause or exacerbate cardiovascular complications (CC), such as heart failure, acute coronary syndromes (ACS), cardiac arrhythmias and strokes.[5,6] As the population ages, this problem tends to worsen. CVD are the leading cause of morbidity and mortality around the globe including the United States.[1] One-third of CVD deaths occur before the age of 75. CVD causes more than 780 000 annual deaths in the United States alone, accounting for 30% of annual Medicare expenditure and 17% of total U.S. healthcare costs.[7,8] It is estimated that by the year 2030, CVD will have a direct medical cost of $818 billion.[9]

Therefore, acquiring a better understanding of the different groups affected by CVD, the causes and direct associations with frequent co-morbidities (e.g. CAP and other infections) and potential strategies to manage these patients is a public health priority. In this review, we summarize current literature on the risk of CC, diagnostic methods, underlying mechanisms, potential effects of medications and role of immunization in adult patients with CAP.

CARDIOVASCULAR COMPLICATION AFTER CAP

Involvement of the cardiovascular system after developing CAP is as an important short- and long-term co-morbidity.[6,10] Corrales-Medina *et al.*[11] performed a systematic review and meta-analysis (SRMA) of observational studies, and found that CC occurred in 18% of CAP patients. Most of the studies showed that the rate of CC is higher among hospitalized patients than outpatients.[11]

Several risk factors are associated with the development of CC in patients with pneumonia. The strongest associated risk factor is preexistent CVD preceding the pneumonia event.[12] Patients with CAP older than 65 years tend to have higher rates of co-morbidities. The most common co-morbidities include chronic

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obstructive pulmonary disease (COPD), ischaemic heart disease, congestive heart failure, diabetes and stroke.[12] However, all these conditions seem to be over-represented among hosts with compromised immunological status, potentially leading to poor clinical outcomes. In addition, many of these co-morbidities are associated with poor functional and disability status, usually requiring admission to long-term care facilities.[13,14]

Multiple studies have shown that CAP patients with advanced age have higher rates of long-term mortality when compared with younger patients with CAP. However, the impact of age as a risk factor is variable, and seems to start as early as 50 years of age or as late as 70 years of age.[13] In addition, gender is also a risk factor for long-term mortality and CVD, which is why both variables are included in the pneumonia severity scores that predict mortality.

Patients with chronic CVD have up to three times increased risk of developing CAP, particularly those with heart failure. Cerebrovascular disease/stroke doubles the risk of CAP. Both conditions are present in up to half and one-third of the patients, respectively.[14] The most important condition associated with prior CVD is atherosclerosis which affects more than one-third of the adult population. More than 50% of atherosclerotic CVD presents as coronary events, including sudden cardiac death, non-fatal myocardial infarction (MI) and revascularization, with the rest as stroke and claudication associated with peripheral arterial disease.

MECHANISMS OF CARDIAC DAMAGE DURING CAP

The exact mechanisms underlying CC in patients with CAP are not fully understood.[5,10] Several researchers have hypothesized that these CC befall as a result of the interactions between demographic characteristics of the patients (e.g. age, co-morbid conditions, obesity, etc.), pneumonia severity and host reactions to the infection of the lower respiratory tract.[11] Once pneumonia is established, the host remains in a relative hypoxaemic state secondary to alveolar consolidation that affects the normal ventilation/perfusion (V/Q) homeostasis.[11] Moreover, pneumonia is a highly pro-inflammatory disease, thus patients with CAP have high circulating levels of cytokines and chemokines that are necessary to control the infection by increasing chemotaxis and generating leukocyte extravasation into the lungs[15]; however, persistent or uncontrolled inflammation could increase tissue damage and malfunction (i.e. heart inotropism is diminished in hearts exposed to high concentrations of cytokines).[16,17] Additionally, circulating endotoxin and some bacterial pathogens have the capacity to activate platelets, generating a pro-coagulant state that could facilitate ACS.[18] Finally, the upregulation of the sympathetic nervous system, a normal response during infections, leads to increased heart rate and vascular resistances that drop cardiac output and coronary perfusion of the heart.[6] The interactions of these phenomena have been proposed as the aetiology of CC during CAP, but the exact mechanism remains a matter of discussion. It is important to highlight that the potentially pathogen-specific damage has not been previously considered as an essential part of the physiopathology of CC during CAP.[5,6,10]

The heart is a very peculiar organ that is composed of several types of cells such as cardiomyocytes (only 30% of the heart), fibroblasts, myofibroblasts, macrophages and other inflammatory cells.[19] Importantly, adults have a regeneration rate of 3% of the total population of cardiomyocytes per year, which severely limits its capacity of healing.[19–21] When cardiomyocytes are killed, myofibroblasts proliferate and synthesize extracellular matrix, rich in collagen, to replace dead cardiomyocytes (i.e. scar formation).[21] This process allows the heart to continue working effectively when the number of dead cells is low, but when the injury is bigger, heart scars are formed and are a potential aetiology of arrhythmias and heart failure.[20] Consequently, identifying the mechanisms underlying cell death and cardiac damage during CAP is of vital importance to understand and prevent CC in patients with CAP. In the following sections, we attempt to describe the translational research available that could potentially describe the host–pathogen interactions and mechanisms underlying CC during CAP (Table 1).

Acute coronary syndromes

ACS refer to a group of pathologies that involve death of cardiac tissue with different clinical characteristics, such as ST segment elevation and non-ST segment elevation MI.[35] In general, it is well accepted that cardiac injury happens after an abrupt interruption of the heart irrigation (i.e. heart ischaemia) following a partial or total occlusion of the coronary blood flow.[35] Epidemiological studies have identified that patients with CAP have an elevated risk of developing ACS, especially in those with previous CVD or coronary risk factors.[12–14] Several epidemiological studies showed that respiratory tract infections are associated with an increased risk of arterial or venous thrombosis leading to ACS or stroke.[36–38] Clayton *et al.* identified all patients of first-diagnosis as MI (n = 11 155) and found 326 patients of respiratory infections during the month preceding the index date.[36] The authors found that patients with a recent respiratory infection had a twofold risk of MI in the 7 days following the infection regardless of the presence of underlying cardiovascular risk.[36] In addition, multiple observational studies have reported variable rates of ACS in patients hospitalized with CAP as high as 11%.[37,39–44]

Atherosclerosis is a pro-inflammatory disease of the endothelium that is characterized by accumulation of lipids in the inner wall of large- and middle-sized arteries, creating plaques that limit the normal blood flow thorough the arterial system.[45,46] Atherosclerosis could remain an asymptomatic disease for several years, but instability and rupture of the plaques lead to local thrombus formation and ACS. Aliberti *et al.* recently reported that CC in CAP patients could be categorized based on whether they are plaque-related or plaque-unrelated events.[47,48] These researchers hypothesized that CAP patients could develop ACS secondary to

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Table 1 Principal pathogen-driven mechanisms of cardiac damage

Pathogen	Injury mechanism	References
Streptococcus pneumoniae	Invade the myocardium and forms microlesions	Brown *et al.*[22] Gilley *et al.*[23] Reyes *et al.*[24]
	Induce ion flow disturbances and electrophysiological abnormalities	Brown *et al.*[22] Alhamdi *et al.*[25] Reyes *et al.*[24]
	Kills cardiomyocytes in a pneumolysin-dependent manner	Brown *et al.*[22] Alhamdi *et al.*[25]
	Generates enlargement and instability of atherosclerotic plaques	Bazaz *et al.*[26]
	Provokes necroptosis in cardiomyocytes and macrophages infiltrating the heart	(Gonzalez-Juarbe N and Orihuela CJ, personal communication with permission) Gilley *et al.*[23] Reyes *et al.*[24]
	Promotes platelet activation	Nel *et al.*[27]
	After antibiotic treatment, induce heart scarring	Brown *et al.*[22] Reyes *et al.*[24]
Chlamydophila pneumoniae	Stimulates the formation of coronary atheromas and instability of preexisting lesions	Pigarevskii *et al.*[28]
	Can infect preexisting atheromas	Pigarevskii *et al.*[28]
Gram negative bacteria	Thrombin formation via PAR during interaction with LPS	Cangemi *et al.*[29]
	Induces platelet activation secondary to LPS and sNOX2-derived peptide interactions	Cangemi *et al.*[30]
Mycoplasma pneumoniae	Produces a pro-inflammatory reaction in the myocardium	Blasi *et al.*[31]
	Decreases left ventricular ejection fraction and increases concentrations of serum troponin	Blasi *et al.*[31]
Neisseria meningitides	Invades myocardial tissue vasculature Facilitates thrombus formation	Bergounioux *et al.*[32]
Francisella tularensis	Translocates into the heart and form microlesions during bacteraemic sepsis Induction of apoptosis in cardiomyocytes Stimulates immune cell infiltration and expression of pro-inflammatory mediators Provokes left ventricular dysfunction and electrophysiological abnormalities	Makara *et al.*[33]
Influenza virus	Acute coronary syndromes with unknown mechanism	Warren-Gash *et al.*[34]

PAR, protease-activated receptor; sNOX2, soluble isoform of the nicotinamide adenine dinucleotide phosphate (NADPH) oxidase.

atherosclerotic plaque destabilization. In this regard, animal experiments of pneumococcal infection have shown that *Streptococcus pneumoniae* can induce enlargement of atherosclerotic plaques and severe endothelial inflammation.[26] Specifically, mice infected intranasally with *S. pneumoniae* were treated with ampicillin for 3 days, after which hearts and brachiocephalic arteries were studied with immunohistochemistry 2 weeks post-infection. Researchers found that animals infected with *S. pneumoniae* had plaques with greater concentrations of activated macrophages and local inflammation, which are markers of plaque instability.[26] Importantly, mouse models of pneumococcal vaccinations have shown that animals which received the vaccinations had greater concentrations of antioxidizing low-density lipoprotein (anti-oxLDL) antibodies, which are known to reduce the size and promote stabilization of atherosclerotic plaques.[49]

Chlamydophila pneumoniae is an obligate intracellular bacterium that is frequently isolated in patients with atypical pneumonia and CAP. *Chlamydophila pneumoniae* has been associated with the aetiology of new atheromas and with the induction of plaque instability.[50] In young apolipoprotein E-deficient (apo E−/−) mice, which spontaneously generate atherosclerotic plaques, a *C. pneumoniae* infection increases plaque size and inflammation.[50] Importantly, *C. pneumoniae* was found to be capable of translocating into atheromas and inducing a severe local inflammation that is well known to generate plaque instability and cardiotoxicity.[50]

Thrombosis formation is another very important mechanism to induce adverse cardiac events during pneumonia; thrombus could block the coronary flow leading to ACS.[51] Thrombus could be generated locally due to a mechanical stimuli and exposure to tissue factors (e.g. secondary to plaque rupture) or spontaneously in the bloodstream during procoagulant states. CAP patients elicit a procoagulant state secondary to an exaggerated host inflammation or by specific

pathogen-driven mechanisms.[10,29] One of the most studied mechanisms of the procoagulant state that presents in infected patients is via protease-activated receptors (PAR). Specifically, its variation PAR1 mediates thrombin generation driven by the tissue factor pathway activation. Normally, this pathway is activated secondary to vascular damage and exposure to the tissue factor; but during infections, high circulating levels of cytokines, endotoxins or the direct interaction with bacterial pathogens lead to activation of endothelial and mononuclear cells, which is a potent stimulus of the tissue factor pathway.[52] Recently, Cangemi *et al.* provided novel evidence that CAP patients have a low grade of circulating endotoxins independent of the aetiological agent.[18] These elevated levels of endotoxins were secondary to increased permeability of the gut that allows endotoxins (including lipopolysaccharides (LPS)) to reach the bloodstream and generate a procoagulant state in CAP patients.[29,53].

Platelets are the first responders to initiate clumping and clotting, especially during blood vessel injuries. A wide variety of stimuli can activate platelets, but the subendothelial collagen and tissue factors are most frequently responsible for triggering platelet activation.[54–56] CAP patients who develop ACS have higher levels of serum biomarkers for platelet activation such as soluble P-selectin (sP-selectin), soluble CD40 ligand and serum thromboxane B2 (TxB2).[29,57] These serum biomarkers represent a procoagulant state secondary to in vivo platelet activation.[29] Further research confirmed that platelets get activated secondary to elevated levels of LPS and a serum biomarker of nicotinamide adenine dinucleotide phosphate (NADPH) oxidase activation, sNOX2-dp.[30,58] Authors concluded that the upregulation of the sP-selectin is secondary to increased levels of bacterial products such as LPS and the pro-inflammatory stimuli of sNOX2-dp. Finally, pneumolysin (Ply), a pore-forming toxin produced by *S. pneumoniae*, has been recently shown to have the capacity to induce platelet activation, as determined by higher levels of sP-selectin in tissue culture experiments.[27]

Troponin I, creatine kinase MB (found mostly in the heart, but small amounts found in skeletal muscles) and heart fatty acid-binding protein (H-FABP) are serum biomarkers of cardiomyocyte death mainly used to diagnose ACS; however, there is a large group of patients with CAP (up to 30%) who do not fulfil the diagnostic criteria for ACS, but have elevated serum concentrations of these biomarkers.[35,59] CAP patients who have mild elevation of troponins without electrocardiogram (ECG) abnormalities are frequently diagnosed as demand ischaemia; which is a transitory elevation of troponins secondary to a mild mismatch between the demand and offering of oxygen to the myocardial tissue.[60] In contrast, there is growing evidence that some specific pathogens can generate direct cytotoxicity that kills cardiomyocytes during pneumonia.

It is well accepted that *S. pneumoniae* and its virulent factors are cytotoxic and even cytolytic during in vitro experiments to several cell groups,[61,62] but data in vivo are unclear. Interestingly, recent research has shown that *S. pneumoniae* could induce programed cell death (i.e. apoptosis) in the heart of mice with invasive pneumococcal disease (IPD).[22] Brown *et al.* demonstrated that mice with IPD developed apoptosis of cardiomyocytes associated with the presence of pneumococcal capsule and Ply in intraperitoneally challenged mice. Additionally, in vitro experiments have demonstrated that *S. pneumoniae* and Ply are capable of inducing apoptosis and pro-inflammatory response.[22,23] *Streptococcus pneumoniae* is also capable of inducing the recently described pro-inflammatory cell death pathway, necroptosis, in lung macrophages and macrophages invading the heart of mice infected with IPD.[23] Importantly, *S. pneumoniae* also kills cardiomyocytes by necroptosis in non-human primates (NHP) with severe pneumonia.[24] These findings are remarkable because they illustrate the capacity of this bacterium to escape from the lungs during pneumonia, reach the heart and induce necroptosis in cardiomyocytes, which could represent a pathogen-driven mechanism for CC during pneumococcal pneumonia (Fig. 1).

Cardiac complications during influenza infection, such as myocarditis, are well recognized, but the role of influenza as a trigger of acute MI is less clear.

Arrhythmias

Heart arrhythmias, specifically de novo or worsening atrial fibrillations, are a frequent early complication of patients admitted with CAP. Corrales-Medina *et al.*[11] reported in an SRMA that the incidence of cardiac arrhythmias was 4.7%, the third most frequent CC in patients with CAP. Most of the patients that develop cardiac arrhythmias are hospitalized, and the incidence is higher among those patients with severe pneumonia (18.5%). Several mechanisms have been proposed to explain the higher incidence of arrhythmias in CAP patients.[5] For instance, Pignatelli *et al.* showed that patients with pneumonia who developed atrial fibrillation during hospital admission had upregulation of the oxidative stress, represented by high serum levels of sNox2-dp.[58]

Some pathogen-specific mechanisms recently reported opened the possibility that these complications are pathogen specific. *Streptococcus pneumoniae* is capable to reach the heart and generate unique microscopic lesions filled with pneumococci in mice with IPD.[22] These lesions were associated with high serum concentration of troponin I and rhythm abnormalities in the ECG.[63] Moreover, in NHP with severe pneumonia, *S. pneumoniae* translocated into the heart, induced necroptosis and diffuse abnormal repolarization, but not clinically relevant arrhythmias.[24] In an elegant study by Alhamdi *et al.*, the authors provided evidence that cardiomyocytes exposed to Ply have a rise in cytosolic Ca^{2+} that appears to play an important role in disassembly of the Vascular endothelial (VE)-cadherin junctions and inducing apoptosis that lead to cardiac damage and arrhythmia.[25]

Heart scarring has been long recognized as an aetiology of cardiac arrhythmias.[19] Recent evidence have shown that mice with IPD that were rescued with antibiotic treatment developed heart scarring as early as 3 days post-infection.[24] More importantly, NHP with severe pneumococcal pneumonia that were saved with

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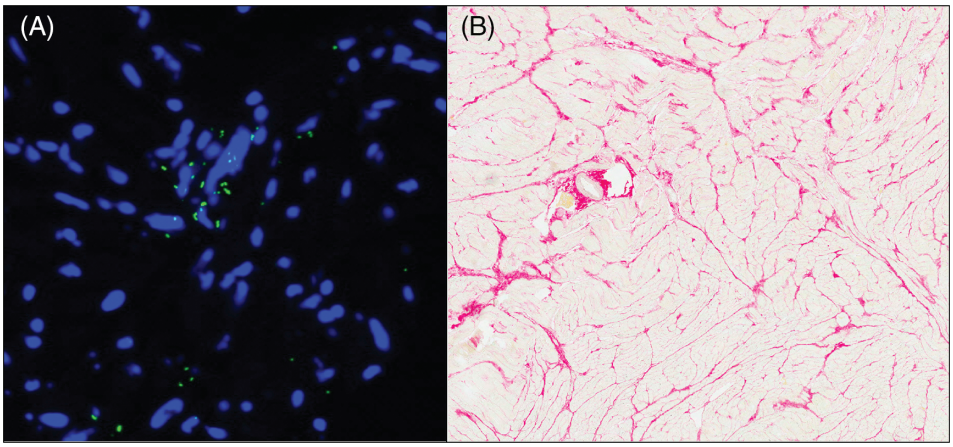

Figure 1 *Streptococcus pneumoniae* escapes the lungs, invades the heart and induces scarring after antibiotic treatment in non-human primates (NHP) with severe pneumococcal pneumonia. Seven NHP were infected intratracheally with *S. pneumoniae* serotype 4 (TIGR 4); four animals were followed until development of severe pneumonia 5 days after infection and three were treated with antibiotics to clear the infection. *Streptococcus pneumoniae* was identified in the myocardium of the four animals acutely infected (A) using immunofluorescence (contra-staining with 4′, 6′-diamidino-2-phenylindole (DAPI), blue colour represents nuclei). In the three NHP rescued, heart scarring was identified using picosirius red staining (B). ■, *S. pneumoniae*; ■, collagen deposition.

antibiotics developed severe heart scarring in comparison to NHP with acute pneumonia or un-infected controls.[24] Therefore, heart scarring after pneumococcal pneumonia represents an important advance to characterize the long-term sequel associated with CAP (Figs 1–2).

Heart failure

Patients with pneumonia have an increased risk to develop heart failure within hospital admission and up to 10 years after hospital discharge. Recent studies have shown that heart failure could be diagnosed in 14% of hospitalized patients and in 1.4% of outpatients with pneumonia.[11] The incidence of heart failure is higher (24%) among high-risk patients with CAP such as those admitted to the ICU compared to low-risk patients with CAP (3%).[11] The mechanisms underlying the development of heart failure after pneumonia are lacking clarity, but researchers have hypothesized that it is in relation with the persistent inflammatory state.[6] C-reactive protein (CRP) is an acute-phase protein synthesized in the liver in response to high levels of serum cytokines such as IL-6. CRP has shown to be frequently elevated in patients with higher cardiovascular risk; specifically, high levels of CRP in healthy populations have been associated with a higher risk of developing ACS.[64] In pneumonia patients, Hedlund and Hansson reported that patients who survive an acute episode of pneumonia have higher serum levels of CRP (mean: 5 mg/dL, 95% CI: 4–6) and higher incidence of ACS.[65]

Mycoplasma pneumoniae is a very small unencapsulated bacteria that is frequently isolated in children with CAP,[66] and in adults, it could cause atypical pneumonia.[2] *Mycoplasma pneumoniae* can generate severe inflammatory reactions in the lungs systemically and in several extra-pulmonary organs during pneumonia (e.g. lungs, kidney, liver, etc.).[31,67] *Mycoplasma pneumoniae* releases multiple metabolic products that work as damage-associated molecular patterns (DAMP), interacting with toll-like receptors and generating activators of the innate immune system, evidenced by high levels of pro-inflammatory cytokines such as IL-6, IL-18, etc. In addition, *M. pneumoniae* interacts with cell immunoglobulins and mucin domains, which is a family of molecules that are expressed on the surface of T-cells; consequently, the *M. pneumoniae* infection and invasion of the heart is associated with a severe inflammatory reaction mediated by T-cell response.[68] This local inflammation has been associated with a decreased left ventricular ejection fraction, high levels of troponin I and incidence of adverse CC during pneumonia.

ANTIBIOTICS WITH INCREASED RISK OF CC

Among the different antibiotics recommended by clinical practice guidelines for the management of patients with CAP, macrolides and fluoroquinolones are not only frequently considered but also associated with cardiovascular toxicity.[69,70] Both are effective at killing most of the respiratory pathogens, but particularly offer coverage for atypical bacteria, such as *Legionella pneumophila*, *M. pneumoniae* and *C. pneumoniae*. Fluoroquinolones are usually recommended as monotherapy for outpatients or hospitalized patients, and in combination with β-lactams for critically ill patients with CAP.[69] Macrolides are recommended in combination with β-lactam antibiotics for hospitalized patients independent of the degree of CAP severity.[69] Multiple observational studies suggest that combination of macrolide with β-lactam antibiotics may benefit patients who are critically ill due to CAP and required ICU admission which may explain the improved outcomes in this group of patients.[71] Macrolide therapy was evaluated

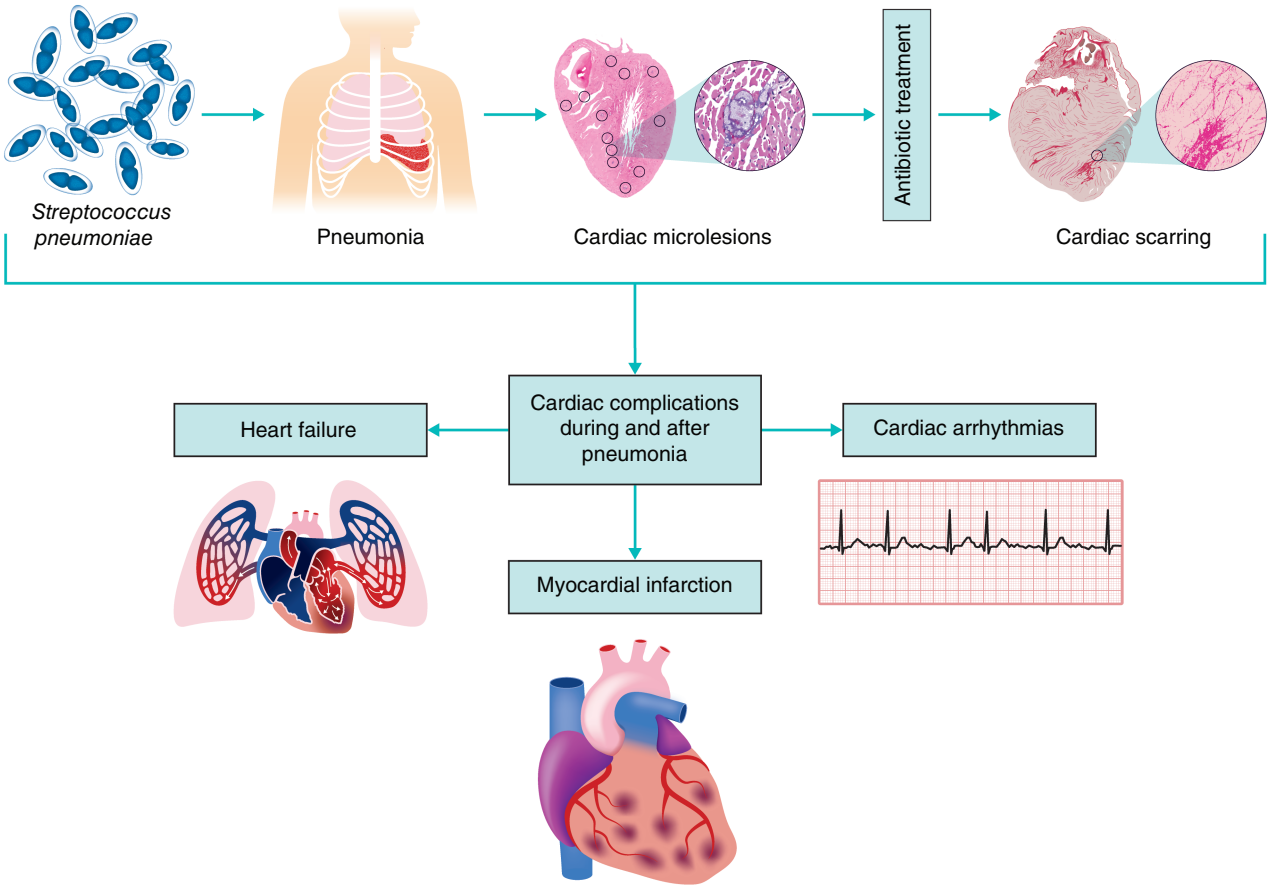

Figure 2 Proposed pathophysiological mechanisms underlying cardiovascular complications (CC) due to pneumococcal pneumonia. This schematic figure represents some of the currently available mechanisms that have been linked to the development of CC driven by *Streptococcus pneumoniae*.

in a recent SRMA of observational studies in critically ill patients with CAP and shown to provide a reduction of mortality when compared with therapies that did not include macrolides (risk ratio (RR): 0.75, 95% CI: 0.58–0.96, $P = 0.02$).[72,73] However, the evidence is based on observational studies without well-designed randomized controlled trials confirming this beneficial effect. Among the different observational studies, the subgroup of patients that presents the highest benefit of treatment with macrolides include those with bacteraemic pneumococcal pneumonia, particularly those with severe CAP.[74–78] It is thought that the macrolide beneficial effect is driven by the immunomodulatory properties.[73] However, there is also evidence suggesting that macrolide antibiotics carry a significant cardiovascular risk.[51] In a large administrative database of older patients hospitalized with pneumonia, the use of azithromycin compared with other antibiotics was associated with a small increased risk of MI, but a lower risk of death within 90 days of pneumonia hospitalization.[79] In addition, a meta-analysis of 33 studies that involved 207 779 963 participants showed that macrolide antibiotics were associated with an increased risk of sudden cardiac death or ventricular tachyarrhythmias, but not an increase in general mortality.[80] This meta-analysis was not limited to patients with CAP, but it remains a real concern that patients with pneumonia who have QT prolongation are at an increased risk of a CC.[80] Therefore, the complexity related to the multiple factors that concomitantly interact at a specific point in time, such as acute infection, host–pathogen interaction and host–pathogen–treatment interaction, highlights the difficulties in the understanding of CC in patients with pneumonia. We recommend that the use of fluoroquinolones or macrolides should be individualized and a careful assessment of the risks and benefits is crucial in the decision-making at the time of selection for the appropriate antibiotic therapies in patients with CAP.

POTENTIAL MEDICATIONS TO PREVENT AND TREAT CC

Several adjunctive therapies have been proposed as preventive or treatment strategies to improve the outcomes of patients with pneumonia.[5] This is a topic of interest that is beyond the scope of this study. However, the different interventions will be mentioned and highlighted accordingly.

Among the different therapies that could potentially prevent the development of CC in patients with CAP are statins, angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARB) and

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anti-platelet agents. Patients at risk are chronically receiving these medications prior to the development of CAP or while they developed CAP. Multiple SRMA based mainly on observational studies have shown that chronic therapy with statins is associated with lower incidence of pneumonia and/or lower CAP-related mortality.[81–86] However, these results are conflictive by heterogeneity, healthy user bias and methodological limitations that preclude drawing a consistent conclusion. It is unclear if this suggested effect is driven by preventing CC due to the immunomodulatory properties observed with statins or the limitations mentioned above. Chronic use of ACE inhibitors has also been associated with improved outcomes in patients with CAP. Caldeira *et al.*[87] reported in an SRMA of 37 eligible studies that ACE inhibitors, but not ARB, were associated with a reduced risk of pneumonia-related mortality when compared with controls. Several subgroups of patients may benefit the most, such as those with prior stroke and of Asian origin. The mechanisms linked to this benefit are unclear due to the circumstances related to patients who are at risk and in whom ACE inhibitors and ARB are formulated. Differences in genetic polymorphisms of ACE among patients of Asian descent may explain the benefits in preventing CAP observed in this patient population.[87]

A less clear effect is observed when statins are started as adjunctive treatment in CAP patients at the time of hospital admission or initiation of care. Studies derived from sepsis or ventilator-associated pneumonia suggest that statins have an increased risk of death when initiated as a coadjutant treatment. The only practical recommendation at this point is that if the patient is chronically taking statins they should be continued during and after the pneumonic event, unless they have contraindications.

IMMUNIZATIONS AND RISK OF CC

It has been suggested from observational studies and SRMA that immunizations may reduce the risk of major CC.[88–92] For more than a decade, the American Heart Association and American College of Cardiology[93] has recommended influenza immunization as part of the comprehensive secondary prevention in patients with coronary and other atherosclerotic vascular diseases. Immunization with live, attenuated vaccine (administered intranasally) was not recommended for patients with cardiovascular conditions. This recommendation is based on evidence derived from cohort and limited randomized controlled trials. A recent SRMA of six randomized controlled trials of 6735 patients confirmed that the influenza vaccination was associated with a lower rate of CC (RR: 0.64, 95% CI: 0.48–0.86).[90] However, the mean follow-up was 8 months, with a vanishing effect after 9–12 months of vaccination. Thus, we could conclude that influenza vaccination may reduce cardiovascular-related mortality and combined CC. However, some studies had some risk of bias, inconsistent results and there is a need for higher quality evidence.

Influenza vaccination is not the only vaccination that is suggested to prevent CC. Vlachopoulos *et al.*[94] identified 11 cohort studies that included 332 267 participants, with a mean follow-up period of 20 months where pneumococcal vaccination was associated with a lower rate of CC (pooled RR: 0.86, 95% CI: 0.76–0.97) and cardiovascular mortality (pooled RR: 0.92, 95% CI: 0.86–0.98). However, they also observed that pneumococcal vaccination was more protective in high cardiovascular risk populations and with older age, and the protective role was attenuated after 1 year. The elderly were the only subpopulation of patients with the highest cardioprotective effect regarding MI and cerebrovascular events.[94] In a second meta-analysis, Ren *et al.*[95] showed that pneumococcal vaccination was also cardioprotective by an unknown mechanism, with conflicting data originating mainly from observational studies with several methodological limitations.

In conclusion, these data suggest that both influenza and pneumococcal vaccines may have important cardioprotective effects, and the benefit may be higher in certain populations at risk, such as elderly patients or patients with co-morbid CVD.

CONCLUDING REMARKS

CC during and after pneumonia are highly prevalent and closely associated with adverse clinical outcomes and increased associated medical costs. Patients with severe pneumonia, previous CVD and older age are at higher risk to develop CC. This pertains to both acute hospitalization and for up to 10 years thereafter. The period of highest risk is in the first 30 days after acute pneumonia. Several pathogen-driven mechanisms of cardiac injury have been proposed and could be the target of future therapeutic intervention to reduce incidence of CC and improve outcomes in patients with pneumonia. Clinicians should be aware of these potentially fatal complications of pneumonia to enable early diagnosis and appropriate treatment.

Disclosure statement

The content is solely the responsibility of the authors and does not necessarily represent the official views of the Department of Veterans Affairs.

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