Review Article

Cardiovascular complications in patients with community-acquired pneumonia

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ABSTRACT

Community-acquired pneumonia (CAP) is the most frequent infectious disease, responsible for a great morbidity and mortality worldwide. It is known that poor outcome in CAP patients is not only directly related to pneumonia but also to comorbidities both during hospitalization and long term after discharge. Evidences show a high correlation between acute respiratory infections and increased risk of cardiovascular events (CVEs), such as acute myocardial infarction, arrhythmias, congestive heart failure, and stroke. The excessive systemic inflammatory response is responsible for hypoperfusion and activation of cytokines causing endothelial dysfunction, pro-coagulant effects, and atheroma instability. An established diagnostic tool to identify high-risk patients is not yet available, but cardiovascular biomarkers seem to be more effective than inflammatory molecules. Early identification of patients at higher risk for CVEs is mandatory to treat them effectively with prophylaxis medications, to establish adequate clinical surveillance and prevention with vaccinations. The present article reviews the epidemiology, pathophysiology, clinical presentation, risk factors, diagnosis, outcomes, and prevention of CVEs in patients hospitalized for CAP.

Key words: Acute myocardial infarction, arrhythmia, cardiovascular events, community-acquired pneumonia, heart failure, stroke

INTRODUCTION

Community-acquired pneumonia (CAP) is still an important cause of morbidity and mortality worldwide, especially in the elderly.[1] In the last decades, mortality rates have not changed, despite advances in diagnostic and supportive methods.[2,3]

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It is now known that poor outcome in CAP patients is not only directly related to pneumonia but also to comorbidities,[2,4] both during hospitalization and after discharge,[5-7] with an absolute rate of events varying broadly from 10% to 30% across different cohorts.[8]

Evidences show a high correlation between acute respiratory infections and increased risk of cardiovascular events (CVEs) [Table 1]. The occurrence of a CVE in a hospitalized patient with CAP may significantly affect clinical status and a severe CVE could be the primary cause of clinical failure.[9,10]

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The aim of this study is to evaluate epidemiology, clinical presentation, physiopathology, outcomes, risk factors, and prevention of CVEs in patients with CAP.

SEARCH STRATEGY AND SELECTION CRITERIA

We searched Medline for papers published from January 1, 2000 to April 30, 2017. We used the search terms "community acquired pneumonia" or "pneumonia," in combination with the terms "cardiovascular events," "acute myocardial infarction," "arrhythmia," "heart failure," "stroke," and their variations. We restricted the search strategy to adults. We also searched the reference lists of articles identified by this search strategy. Review articles and book chapters are cited to provide readers with more details and more references.

EPIDEMIOLOGY

Different epidemiological and primary care studies demonstrated an increased risk of CVEs in the first 3 months after an acute respiratory infection.[17-20] The increased risk for cardiac events in hospitalized patients may be 8 folds higher in the first 15 days from admission and reach 100 folds within the first 2–3 days.[21] At long-term follow-up of patients with a previous episode of CAP, studies reveal that cardiovascular mortality contributes to 30% of deaths.[2,7,22,23]

A study by Musher *et al*. including 170 patients found that 19.4% of patients hospitalized with CAP developed cardiovascular complications such as acute myocardial infarction (AMI), severe arrhythmias, or acute congestive heart failure (CHF).[15] Another study by Ramirez *et al*. found that 15% of patients with AMI on admission had severe CAP.

Table 1: More recent studies on cardiovascular events and community-acquired pneumonia

Author	Year of publication	Study	Number of patients enrolled	Incidence/ prevalence of CVEs	Risk factors	Outcomes
Griffin *et al*.[11]	2013	Retrospective cohort study, 80 centers in 13 countries	3068 inpatients with CAP	376/3068 (12%)	Hyperlipidemia Severe CAP *Staphylococcus aureus* infection *Klebsiella pneumoniae* infection	In-hospital mortality 28% 28 days from admission, mortality 36%
Cangemi *et al*.[12]	2015	Prospective observational study, Italy, university hospital	301 consecutive patients with CAP	In-hospital mortality: 55/301 (18%) Follow-up: 73/301 (24%)	During follow-up Age, hypertension, diabetes mellitus Baseline values of TnT Intrahospital cardiac complications	In-hospital mortality 32%
Mandal *et al*.[13]	2011	Retrospective observational study, Scotland, five hospitals	4408 patients with CAP	Stroke 2.2% AMI or ACS 5% New-onset AF 9.3%	Stroke: Age, prior history of stroke AMI: Age, previous AMI, COPD, chronic renal disease AF: Age, diabetes mellitus, prior AMI	90-day mortality 13.9% LOS 12 days
Corrales-Medina *et al*.[14]	2012	Prospective observational study, USA, 5 medical institutions	1343 inpatients with CAP 944 outpatients with CAP	358/1343 (26.7%) 20/944 (2.1%)	Older age Nursing home residence History of heart failure Prior cardiovascular disease Tachypnea Acidosis High urea levels Anemia Hyponatremia Pleural effusion Inpatient care	30-day mortality 15.3%
Musher *et al*.[15]	2007	Prospective observational study, The USA, The Veterans Medical Center	170 patients hospitalized with pneumococcal pneumonia	33/170 (19.4%)		In-hospital mortality CAP and AMI 40% CAP and new-onset arrhythmias 0% CAP and CHF 30%
Aliberti *et al*.[16]	2015	International multicenter prospective cohort study	905 consecutive patients hospitalized with CAP	AMI: 21/205 (2.3%) Other CVEs: 107/905 11.7%	AMI: Female sex, liver disease, severe sepsis Other CVEs: Female sex, age >65 years, neurological disease, pleural effusion	In-hospital mortality AMI: 43% Other CVEs: 21%

CVEs: Cardiovascular events, CAP: Community-acquired pneumonia, AMI: Acute myocardial infarction, ACS: Acute coronary syndrome, AF: Atrial fibrillation, COPD: Chronic obstructive pulmonary disease, LOS: Length of stay, CHF: Congestive heart failure

During hospitalization, among patients with clinical failure, 20% of cases developed CVEs.[24]

A retrospective cohort study of 206 patients followed up to 15 days after discharge showed that 11% of CAP patients had acute coronary syndrome, with an 8-times higher risk for occurrence of CVEs in comparison to controls.[25]

CLINICAL PRESENTATION

Acute myocardial infarction

Occurrence of AMI or unstable angina is reported to be 5% among patients with pneumonia in a recent meta-analysis.[26] Mechanisms causing myocardial ischemia (plaque rupture and *in situ* thrombus formation) are triggered or worsened during acute pneumonia.[8] A multicenter, prospective observational study published in 2015 found that AMI had a prevalence of 2.3% versus 11.7% of other CVEs, but it was associated with a significantly higher severity of the disease on admission and a significantly higher in-hospital mortality (43%).[16] In addition, this study showed that female sex, severe sepsis, and previous history of liver disease are independent risk factors for the occurrence of AMI.

Clinicians should promptly identify patients with CAP at risk for AMI, to give them adequate cardiovascular therapy, such as acetyl-salicylate acid, and to strictly monitor them for ischemic events both during and after the resolution of the acute infection.

Arrhythmias

Several explanations have been proposed to justify the association between acute respiratory infections and the risk of arrhythmias. Some studies refer to the increased levels of inflammatory cytokines in serious infections[24] or to disturbed hemodynamic homeostasis, pro-thrombotic conditions, and increased catecholamine release.[21] Other studies describe a direct inflammatory effect on coronary arteries, myocardium, and pericardium, as well as direct infection of cardiomyocytes, as provocative mechanisms of acute arrhythmias.[27-33] Finally, acute disturbances, such as hypo/hyperthermia, electrolyte abnormalities, and hypoxemia, may cause arrhythmias.

A study by Soto-Gomez *et al*.[34] found new-onset arrhythmias in 12% of cases among a large number of patients with pneumonia, especially in severe and elderly patients. In addition, authors found that arrhythmias were associated with an increased 30- and 90-day mortality. Older age, CHF, and septic shock were independently associated with the onset of arrhythmias. On the contrary, use of beta-blockers prior to admission seemed to prevent arrhythmias, thanks to their pharmacological effect.[34]

Further studies in this field are needed to understand how long these patients remain at risk for arrhythmias after acute pulmonary infections, which could be the causative mechanism and what kind of therapy may be prophylactic against these CVEs.[34]

Heart failure

Incidence of new or worsening CHF is the most frequent cardiac complication among patients with pneumonia. A meta-analysis by Corrales-Medina *et al*.[26] reported an incidence of CHF of 14% versus 5.3% of acute coronary syndrome and 4.7% of arrhythmias. Results also show an association between CHF and female sex, older age, and preexisting coronary artery disease.[26]

Studies with a high prevalence of chronic obstructive pulmonary disease (COPD) and pneumonia found a higher incidence of CHF.

Stroke

Association between stroke and acute respiratory infections seems to be known. A case–control study published in 2009 demonstrates that patients who suffered from stroke had a significantly higher incidence of respiratory infections in the year before CVEs, especially CAP. Furthermore, in multivariable analysis adjusting for major vascular risk factors, respiratory infection was independently associated with stroke.[35]

Physiopathology

During an acute respiratory infection, inflammation is both local and systemic in the lungs. Thus, inflammatory processes and molecules can affect other organs, such as the heart. Locally, ventilator-perfusion mismatching and intrapulmonary shunt cause hypoxemia. On the other side, a significant systemic inflammatory response may cause severe hypoperfusion with a consequent multiorgan failure.[36,37] This systemic process is mediated by the high levels of pro-inflammatory cytokines that cause endothelial dysfunction, atheroma instability, rupture of the atheromatous plaque, increased fibrinogen levels, and prothrombotic vascular conditions[38-40] [Figure 1].

The majority of cardio- and cerebro-vascular events are associated with platelet activation.[41] One of the mechanisms consists in the interaction between platelets with neutrophils and vascular endothelium. Adhesion of neutrophils to activated vascular endothelium provokes anti-inflammatory activities of endothelial cells, exacerbating microvascular coagulation.[42,43] In bacterial CAP, it seems to exist an interaction between Gram-positive cell wall or Gram-negative endotoxin and receptors expressed by platelets, which activates fibrinogen cascade, production of thromboxanes, and consequent aggregation of platelets and vasoconstriction. In particular, some *Staphylococcus* and *Streptococcus* strains seem to have this property on platelets, mediated by CXC chemokine which also has antibacterial activity.[44,45] In animal models of invasive

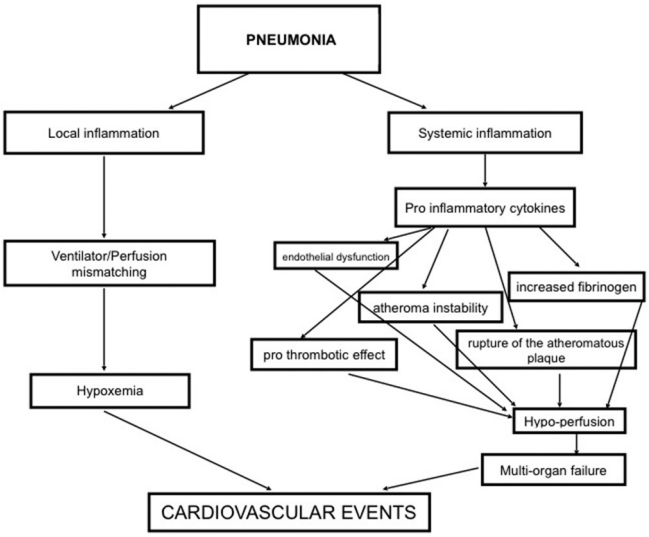

Figure 1: Pathogenesis of cardiovascular events in community-acquired pneumonia

pneumococcal disease, *Pneumococcus* cause microlesions into the myocardium that affect cardiac function.[45,46]

DIAGNOSIS

Since an established tool to estimate long-term outcomes of CAP patients is still unavailable, several studies address the topic of biomarkers as screening tests for the presence of structural heart diseases or for short- and long-term prognosis in CAP. Actual evidences seem to show that cardiovascular biomarkers are more effective predictors of mortality than inflammatory biomarkers, both in short and long-term follow-ups. This could be explained by different reasons. Cardiovascular biomarkers are increased during sepsis, which is a known risk factor for a poorer outcome in CAP patients. In addition, they can reveal the underlying preexisting cardiac disease or septic cardiomyopathy, which may be aggravated by acute inflammatory activation caused by pneumonia.

CAPNETZ studies (the German Competence Network for Community-Acquired Pneumonia) addressed, in particular, this topic. Pro-atrial natriuretic peptide and pro-vasopressin (copeptin) levels were significantly independently associated with short- and long-term mortality among 1170 CAP patients, in comparison to inflammatory markers.[47] Further studies showed that proadrenomedullin had the best performance and the strongest independent correlation to short- and long-term mortality[48] and was a good prognostic factor for mortality almost 1 year after discharge from hospital,[49] probably because of its multiple functions, such as cardiovascular activity, anti-inflammatory and antibacterial functions.

The use of these cardiovascular biomarkers could help in identifying patients at higher risk for CVEs and mortality, who may need a closer medical follow-up for complications.

Another potential diagnostic tool consists in the measurement of cardiac autonomic control (CAC), assessed by heart rate variability, as an altered sympathovagal balance, may play a role in the occurrence of CVEs during CAP and it is associated with poor outcomes.[16,50-53] An Italian multicenter study published in 2016 hypothesized that a deregulation of CAC with a reduction of total variability and loss of sympathetic rhythmical property could be related and/or predict CVEs and mortality in CAP patients.[54] Authors found an alteration of CAC on CAP patients, especially severe cases, consisting in a lower sympathetic modulation, and a predominant parasympathetic oscillatory rhythm, suggesting that these measurements could be useful to stratify patients by severity and cardiovascular risk.

OUTCOMES

Patients admitted with CAP who present or develop a CVE are at higher risk for in-hospital and long-term mortality. An observational cohort study of 500 patients with CAP found that all CVEs together were the first cause of clinical failure related to CAP.[55] A more recent multicenter prospective study showed increased mortality in patients with CAP with CVEs compared with those without CVE (15.3% *vs*. 2.8%, respectively; odds ratio, 3.5; 95% confidence interval [CI], 2.3–5.2).[26]

In-hospital mortality

The study by Ramirez *et al*. disclosed that patients who developed AMI had a longer time to clinical stability and length of stay and a significantly higher rate of clinical failure and in-hospital mortality in comparison to patients without AMI (52% *vs*. 11% and 28% *vs*. 7%, respectively).[24]

Thirty-day follow-up

The same observational study cited before showed an increased mortality in patients with coronary artery occlusion and AMI also at 30 days after discharge (31% *vs*. 10%, respectively).[24] Another study by Viasus *et al*. reported that CVEs were independently associated with 30-day mortality, with an odds ratio of 2.18 (95% CI, 1.38–3.42).[10] Occurrence of a CVE in an early phase of pneumonia is associated with a lower rate of survival at 30 days from hospital admission also in another study in 2012.[14]

Long-term follow-up

Patients hospitalized with CAP are known to have a higher risk of long-term mortality.[5,56] Several studies found CVEs as one of the main causes of long-term mortality among these patients. A study published by Yende *et al*. reported CVEs as the first cause of death over 1 year after an episode of pneumonia, along with higher levels of inflammatory markers, especially interleukin (IL)-6, suggesting that a persisting inflammatory response may have some role in the increased risk for mortality in this population.[22] In another study conducted in Canada, CVEs were the second cause

of re-hospitalization after a first episode of pneumonia in 5-year follow-up.[7] A study by Mandal *et al*. underlined the association between CVEs and cerebrovascular disease and increased mortality at 90 days among 4408 patients hospitalized with CAP.[13] An Italian study published in 2015[12] found that almost 50% of patients who died during the follow-up had intrahospital cardiac complications, confirming that intrahospital cardiac complications increase the risk of mortality not only after a short-term but also after a long-term follow-up.

RISK FACTORS FOR CARDIOVASCULAR EVENTS

To prevent CVEs, it is important to promptly identify patients at risk, as these events are still underdiagnosed.[14,13] Many risk factors were identified in literature. In a large prospective cohort study of patients hospitalized for CAP, the presence of age >65 years, chronic heart disease, tachycardia, septic shock, multilobar pneumonia, hypoalbuminemia, and pneumococcal pneumonia were independent predictors of acute cardiac events.[10] Moreover, some authors have created a practical clinical score to stratify the risk of acute cardiac events in these patients. The low- and moderate-risk groups had rates of positive events of 0 and 4.4% and 9.5 and 9.9%, respectively, and the high-risk group had a rate between 18.7% and 34.6%, with a good accuracy (area under curve 0.73).[10]

Other studies on CAP have found that the major risk factors for CVEs are older age, nursing home residence, preexisting chronic respiratory or cardiovascular conditions, severity of CAP, and smoking.[21] Recently, Corrales-Medina *et al*. also reported that older age, nursing home residence, a history of heart failure, prior cardiac arrhythmias, previously diagnosed coronary artery disease, arterial hypertension, tachypnea, acidosis, elevated urea, hypernatremia, anemia, pleural effusion, and inpatient care were factors independently associated with CVEs. Similarly, in another study, risk factors for AMI were age, previous AMI, COPD, and chronic renal disease.[14] In addition, age, diabetes mellitus, and prior AMI were predictors of atrial fibrillation. Griffin *et al*. demonstrated that, apart from age, also a history of hyperlipidemia, pneumonia severity, or causative pathogens such as *Staphylococcus aureus* or *Klebsiella pneumoniae* were associated with an elevated risk for CVEs.[14]

ADJUNCTIVE TREATMENTS

Different adjunctive therapies with anti-inflammatory and antiplatelet effects have been studied in patients with CAP at risk for CVEs [Table 2].

Macrolides

Macrolides are now widely known as immunomodulatory medication, already used in chronic respiratory diseases such as bronchiectasis, asthma, COPD, and diffuse panbronchiolitis.[73] Use of macrolides in CAP is not established yet, but some studies showed that they can improve clinical outcome in sepsis.[74,75] Macrolides not only possess anti-inflammatory and immunomodulatory activities, but also possess an inhibitory activity on platelet-activating factor (PAF) that mediates platelet aggregation.[57] Patients with CAP, especially with severe presentation, treated with macrolide-based antibiotic regimens, have been reported to have clinical benefit on outcomes.[76,77] On the contrary, a study published in the UK in 2013 found that the use of clarithromycin in CAP patients was independently associated with higher risk of CVEs, increasing with the duration of treatment.[78]

Corticosteroids

The evidence for corticosteroids as an adjunctive therapy in CAP (usually in severe CAP and septic shock) is still controversial.[58-62]

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*.[63]

PREVENTION

Medical aspect

Some medications normally used in standard therapies for cardiovascular diseases seem to have a potential positive effect on systemic inflammation and incidence of CVEs in CAP patients [Table 2].

Statins might reduce mortality in CAP patients by their immunomodulatory effect and plaque stabilization properties.[64,65] They seem to have anti-inflammatory and antioxidative effects, improvement of endothelial

Table 2: Adjunctive and preventive therapies for patients with community-acquired pneumonia at risk for cardiovascular events

Therapies	Therapeutical Activities
Macrolides	Anti-inflammatory and immunomodulatory activities[57] Inhibitory activity on PAF that mediates platelet aggregation[57]
Corticosteroids	Anti-inflammatory activity[58-62] Inhibition of platelet activation[63]
Statins	Anti-inflammatory and antioxidative effects[64,65] Improvement of endothelial function[64,65] Increased nitric oxide bioavailability[64,65] Suppress platelet activation[66] Reduction in release of pro-inflammatory chemokines and cytokines[64,65]
ACE inhibitors	Anti-inflammatory activity[67] Protective effect on the lung by decreasing renin-angiotensin system[68,69]
Antiplatelet agents	Protective in severe sepsis and septic shock[26,70] Inhibition of platelet aggregation[26,70]
Vaccines	Influenza vaccine[71] Anti-pneumococcal vaccine (PCV, PPV23)[72]

ACE: Angiotensin-converting enzyme, PCV: Pneumococcal conjugate vaccine, PPV23: Polysaccharide 23 vaccine, PAF: Platelet-activating factor

function, and increased nitric oxide bioavailability. The anti-inflammatory effect seems to decrease the rate of incidence of severe sepsis in patients with CAP pretreated with statins, subsequently improving the survival rate.[79,80] In addition, statins have been reported to suppress platelet activation by various mechanisms, which also appear to be largely attributable to inhibition of hydrated to o-methyl-8-hydroxybutyryl CoA reductase.[66] A systematic review evaluated the immunomodulatory effects of statins in patients with CAP and found a reduction in the release of pro-inflammatory chemokines and cytokines in patients with CAP, in both the pulmonary and systemic compartments.[81] Moreover, authors found a decreased risk of pneumonia and an improved survival of pneumonia in patients taking statins.[81]

Angiotensin-converting enzyme (ACE) inhibitors also seem to reduce 30-day cardiovascular mortality in CAP.[82]

A retrospective study published in 2013 suggests that the beneficial effects of statins, ACE inhibitors, and angiotensin II receptor blockers are due to other mechanisms other than preventing future CVEs.[83] For example,[84,85] anti-inflammatory response of both statins and ACE-I, antibacterial and antiplatelet activities of statins,[67] and protective pulmonary effect showed by ACE-I, as an increased activity of the renin–angiotensin system, are associated with a higher incidence and mortality from acute respiratory distress syndrome.[68,69]

Antiplatelet drugs may also be protective in severe sepsis and septic shock. Nevertheless, there are few studies evaluating their potential benefits on CAP outcomes.[26] A study by Cangemi *et al*. found no effect of aspirin administration on the occurrence of CVEs in CAP patients.[12] On the contrary, in a retrospective study of 886 patients in Intensive Care Unit, patients who received acetyl-salicylic acid had a significantly lower in-hospital mortality.[70]

Vaccines

Influenza and pneumococcal vaccinations are the two main available prophylaxes for respiratory infections and are highly recommended for patients affected by chronic cardiovascular diseases.

Studies are available regarding the association between influenza vaccination and a reduction in AMI and stroke.[74,73] A large multicenter study of 31,546 high-risk patients of at least 55 years showed an association between influenza vaccination and a lower cardiovascular risk during influenza season, when the circulating influenza matched the vaccine antigen.[71]

Studies regarding the association between pneumococcal vaccination and CVEs are conflicting, and by now, there are no randomized controlled trials on this topic. Some observational studies failed to find a positive association between pneumococcal vaccination and decreased CVEs.[86,87]

A large prospective population-based study to evaluate the effectiveness of the polysaccharides 23 vaccine against myocardial infarction and stroke found a marginally significant reduction in the adjusted risk of ischemic stroke (35%, 95% CI: 1%–58%), suggesting a possible protective role of vaccination against some acute thrombotic events. No protective effect was found for AMI in this population.[72]

On the contrary, a Chinese study found that patients who underwent both influenza and pneumococcal vaccinations had a significantly lower mortality for stroke and AMI.[88]

A systematic review and meta-analysis conducted in 2015 evaluated 332,267 patients with pneumococcal vaccine, followed up for 20 months. Results showed that vaccinated patients have a significantly lower risk by 14% for total CVE events and 8% for cardiovascular mortality, especially in older patients and in patients at major cardiovascular risk.[89] Vaccination were proved to be more effective in this cohort with a high frequency of cardiovascular comorbidities or COPD.

CONCLUSIONS

The occurrence of CVEs in patients presenting with CAP is frequent both during acute respiratory event and after its resolution, up to even 1 year after hospitalization. They carry a worse prognosis and a higher short- and long-term mortality. It is mandatory to evaluate every single patient for risk factors for CVEs, identifying the subgroup of high-risk patients in which diagnostic methods, closer monitoring, and preventive strategies may be considered.

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Conflicts of interest

There are no conflicts of interest.

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