REVIEW
Cardiovascular Complications of Community-Acquired Pneumonia

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Abstract. Pneumonia is a highly encountered acute respiratory infection that can be caused by different pathogenic agents, including mostly viruses but also bacteria, fungi, and parasites. Cardiovascular complications frequently occur in CAP patients during hospitalization, with an absolute rate of cardiovascular events ranging from 10% to 30%. The cardiovascular system can be affected by multiple mechanisms induced by such an acute infection as CAP, which can cause cardiovascular complications such as heart failure, cardiac arrhythmias, acute coronary syndromes, and venous thromboembolism. These complications can be prevented by evaluating the pathophysiology of cardiac events in these patients based on atheroma plaque-related events, such as acute myocardial infarction, or events unrelated to plaque, such as arrhythmias and heart failure. Cardiovascular problems can impact patients' quality of life for a long period of time, up to one year of hospital discharge, and they are highly associated with adverse clinical outcomes and increased associated medical costs.

Keywords: *pneumonia, cardiovascular complications, arrythmia, patherosclerosis, Streptococcus pneumoniae*

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1. Introduction

Pneumonia, one of the most frequently encountered infections, is defined as "new lung infiltrates plus clinical evidence that the infiltrate is of an infectious origin, which includes the new onset of fever, purulent sputum, leukocytosis, and a decline in oxygenation" [1].

Community-acquired pneumonia (CAP) represents one of the leading causes of morbidity and mortality worldwide, gradually becoming one of the most common and deadly respiratory infections throughout Western countries, affecting all categories of patients, including both immunosuppressed and healthy patients [2,3].

CAP is the second most common cause of hospitalization and the most common infectious cause of death, and almost 9% of patients hospitalized with CAP will be rehospitalized due to a new episode of CAP during the same year [4]. Due to its extensive spectrum of associated clinical features, ranging from fever and productive cough to respiratory distress and sepsis, CAP represents an important differential diagnosis among all respiratory illnesses [3,4].

One of the most important **risk factors** that must be taken into consideration in the case of CAP are:

- *Age:* The incidence of CAP requiring hospitalization rises with age, and approximately 1 in 3 patients hospitalized with CAP doesn't survive within one year [5, 6]. The annual incidence of hospitalization for CAP among adults

between 65 and 79 years old, the main age category that is affected, is approximately 63 per 10,000 in the United States, and in those 80 years of age or older 164.3 cases per 10,000 adults) [5].

- *Chronic comorbidities:* There are numerous comorbidities associated with an increased incidence of CAP, including chronic heart disease (particularly congestive heart failure), lung diseases (asthma), malnutrition, and immunocompromising conditions. Chronic obstructive pulmonary disease (COPD) represents the main chronic disease that is encountered in patients with CAP, with an annual incidence of 5832 per 100,000 in the United States [6].
- *Respiratory tract infection:* Respiratory infections may lead to viral or secondary bacterial pneumonias, and the most frequently encountered organisms include influenza virus, rhinoviruses, respiratory syncytial virus (RSV), parainfluenza virus, human metapneumovirus, respiratory adenoviruses, and coronaviruses. The incidence of particular viral infections fluctuates seasonally, with the peak of influenza in the winter and enteroviruses in the summer and autumn [7,8].
- Impaired airway protection, alteration in consciousness (e.g., due to stroke, seizure, anesthesia, drug or alcohol use), dysphagia caused by esophageal lesions, or dysmotility are conditions that may lead to aspiration pneumonia or CAP [8].
- *Lifestyle factors,* including smoking and alcohol usage, and exposure to environmental toxins (e.g., solvents, paints, or gasoline) [8–10].

For a better understanding of CAP, based on **the site of acquisition**, pneumonia may be divided into the following categories:

- Pneumonia that presents sooner than 2 days should be regarded as CAP;
- Nosocomial pneumonia, which is a lower respiratory infection that was not incubating at the time of hospital admission and that presents clinically 2 or more days after hospitalization. This type of pneumonia encompasses hospital-acquired pneumonia (HAP) and ventilator-associated pneumonia (VAP).
- HAP refers to pneumonia acquired ≥48 hours after hospital admission, while VAP refers to pneumonia acquired ≥48 hours after endotracheal intubation.
- Health care-associated pneumonia (HCAP), referred to as pneumonia acquired in health care facilities (e.g., nursing homes, hemodialysis centers) or after recent hospitalization, is a term that is no longer used, and patients previously diagnosed with HCAP should be treated similarly to those with CAP. In time, this categorization has led to an increased usage of antibiotics, so it was withdrawn [4-11].

CAP represents one of the most common conditions encountered in clinical practice, and despite all recent medical advances, the morbidity and mortality for CAP still persist very high. The mortality of CAP depends on the clinical setting in which it is treated. In patients not requiring ICU care, the mortality rate is around 3%, and it increases by 25% in intubated patients and almost 50% in ICU patients who require vasopressors [12,13]. Consequently, the in-hospital case fatality rate for this type of patient still remains very elevated. The cardiovascular system can be affected by multiple mechanisms induced by an acute infection, such as CAP, and it can cause cardiovascular complications such as heart failure, cardiac arrhythmias, and acute coronary syndromes [3]. More than half of the elderly patients who present to the hospital with CAP have preexisting chronic cardiac conditions, and the pathophysiology of CAP-related cardiovascular complications includes the process of atherosclerosis, which can lead to endothelial injury and myocardial ischemia or dysfunction [14,15].

CVD represents the main cause of morbidity and mortality around the globe, including the United States [16]. CVD causes more than 780,000 annual deaths in

the United States alone; one-third of CVD deaths occur before the age of 75 years [17]. A medical cost of $818 billion is estimated to be due to CVD, representing an immeasurable burden to the health-care system [18]. The most recent medical studies have indicated that a large part of the patients admitted with CAP will suffer a cardiovascular event. Despite the fact that the spectrum of cardiovascular complications that can occur is extensive, including both deep venous thrombosis and stroke, there is a narrow spectrum of more frequently seen complications. These include acute myocardial infarction, the new onset or worsening of heart failure, and acute myocardial infarction. Although these cardiac events can occur in all types of patients, significant research has been done in order to identify the pathogens most likely involved in CAP associated with cardiovascular events [19].

2. Cardiovascular complications after CAP

Worldwide, the most common cause of death and disability is considered to be coronary artery disease [20]. The association between CAP and cardiovascular complications represents a theme that has been broadly deliberated, especially during the last few decades, and it depends on several factors. Cardiac arrhythmias, including tachyarrhythmias, atrial fibrillation, and malfunction of cardiac conduction, occur more frequently than initially considered [2]. Furthermore, one of the most recent studies proves the minimal or no association between urinary tract infection and acute cardiovascular events, suggesting that the increased risk for cardiovascular events may be specific to respiratory infections [3, 21–23].

1.1. Ischemic events

Numerous mechanisms have been taken into consideration in order to explain how CAP affects the cardiovascular system and to explain the higher incidence of arrhythmias, heart failure, and organ dysfunction in patients admitted with CAP. As Aliberti et al. recently reported, these cardiac malfunction events could be categorized by taking into consideration the atherosclerotic plaque status, classifying them as plaque-unrelated or plaque-related events [2].

Atherosclerosis is the process of plaque formation, which includes various cells, lipids, and debris tissue in the vascular intima, leading in time to atheroma plaque formation. Until the stenosis produced by the atheroma plaque exceeds 70 to 80 percent of the luminal diameter, this process is generally asymptomatic. Atherosclerotic plaques are composed of a lipid core that is separated from the vessel lumen by a cap of fibrillar collagen. The cap rupture exposes the underlying lipid-rich core of the plaque, which is highly pro-thrombotic, resulting in thrombembolism. A myocardial infarction can occur under two conditions: in those patients with atherosclerosis where plaque rupture and thrombosis occur (type I), or in cases of a lack of myocardial oxygen supply in the context of an acute illness (type II). In the scenario of an acute occlusion of one or multiple large epicardial coronary arteries, if time exceeds 40 minutes, it will lead to myocardial infarction [24]. The occlusion, usually thrombotic, leads to oxygen depletion in the myocardium, which causes sarcolemmal disruption and myofibril relaxation. The prolonged ischemia ultimately results in necrosis of myocardial tissue, with the necrosis spreading from the sub-endocardium to the sub-epicardium [20,24]. This process is initiated by endothelium dysfunction, followed by a cascade of events such as the accumulation of lipids, fibrous elements, and calcification, which will result in vessel narrowing and the activation of inflammatory pathways [2,3,19,25,26].

During an episode of pneumonia, all these processes may be triggered or even worsened by the respiratory infection, either directly through pro-inflammatory cytokines or by bacterial proliferation, affecting the cardiovascular system

[2,27,28]. An increased number of patients were observed to develop cardiovascular complications after respiratory infections for up to 90 days. The results have shown that CAP increases the risk of acute cardiovascular events by almost 40% after a 1-year follow-up. According to a meta-analysis, 5% of individuals with pneumonia had either an AMI or unstable angina [3,21-23,29,30].

The researchers above hypothesized that CAP patients could develop cardiovascular complications secondary to pathogen-driven mechanisms. The most frequently detected viruses in patients with CAP are influenza viruses, rhinoviruses, respiratory syncytial virus (RSV), parainfluenza viruses, human metapneumoviruses, respiratory adenoviruses, and coronaviruses. Nevertheless, it needs to be taken into consideration that multiple viral pathogens are encountered in many patients [21, 23].

The most common cause of CAP and sepsis is *Streptococcus pneumoniae* [31]. A cohort study revealed that patients who suffer an infection with *Streptococcus pneumoniae* have an increased risk of acute coronary syndrome in the long term and also have a higher risk of cardiac events in the next 2 weeks after hospital discharge [32].

Animal experiments with *Streptococcous pneumoniae* infection proved that it is capable of invading also the myocardium, leading to necroptosis in cardiomyocytes and microlesions. This bacteria can also provoke electrophysiological abnormalities by causing a disturbance in the ion flow and causing instability in the atherosclerotic plaques. Cardiomyocyte contractility appears to be inhibited in vitro after exposure to the purified *Streptococcus pneumoniae* cell wall, and *Streptococcus pneumoniae* in the bloodstream is also capable of translocation into the myocardium. Both experimentally infected nonhuman primates and two of nine human postmortem cardiac samples from people who died of invasive pneumococcal illness showed proof of microlesion development [33].

The risk of ischemic complications is five times higher, and the risk of stroke is ten times higher during the first 2 weeks after diagnosis, lasting for at least one month, during COVID-19 [34]. COVID-19 is related to an increased risk for ischemic complications, and in recent studies, heart failure was described in 11.5% of patients affected by this virus, contributing to a higher mortality rate. Acute myocardial infarction is found in 7–17% of COVID-19 patients, with a heterogeneous etiology [35].

Taking into consideration the adenoviral and enteroviral genomes, it was detected in 26% of newly diagnosed patients with idiopathic left ventricular dysfunction and in up to 13% of patients with idiopathic dilated cardiomyopathy [36].

Studies have shown that both influenza and pneumococcal vaccines may have an important beneficial impact on certain populations at risk, such as elderly people and patients with important cardiovascular comorbidities [3].

1.2. Prothrombotic status in CAP

The plaque-unrelated events can be divided into two categories, considering the direct lung damage and hypoxia caused by CAP and, moreover, the systemic inflammation may be a key driver of the increased risk of new AF in these patients, as observed also in a recent clinical trial that included 32,689 patients, of which 3,919 (12%) had a new diagnosis of cardiac arrhythmia within 90 days of admission [37]. As in pneumonia, the ventilation or perfusion is disturbed; this clinical modification induces myocardial dysfunction, which causes reduced myocardial contractility, a greater myocardial oxygen demand, and a lower myocardial oxygen supply, leading to heart failure, all of which are caused by the so-called „systemic inflammatory syndrome," which can finally lead to severe

hypoperfusion and multiorgan failure, evolving to sepsis and/or septic shock [38–40].

Additionally, CAP is a pathology that activates a pro-thrombotic status that can induce systemic coagulation abnormalities, including clotting activation (due to an increased activity of the thrombin-antithrombin complex, plasminogen activator inhibitor), and inhibition of anticoagulant factors [41]. Respiratory infections augment the risk of both venous thromboembolism and pulmonary embolism by not only platelet activation and up-regulated synthesis of pro-coagulant proteins, but also by the imbalancement produced in the process of fibrinolysis and the anticoagulant function of the endothelium. Moreover, in immobile critically ill patients who are undergoing mechanical ventilation, venous stasis also amplifies the risk of thromboembolic events. It also needs to be acknowledged that not only the activation of cytokine storms, but also local inflammatory reactions, for example, in the lungs, perdispose to the rupture of endothelial cell membranes, which is followed by vascular thrombosis and increased angiogenesis [42-44].

Moreover, renal dysfunction represents another risk factor with a high impact on the mortality of patients with HF. Acute renal impairment negatively influences heart failure by changing the mechanisms of the sympathetic nervous system, the renin-angiotensin-aldosterone system (RAAS), and dysregulated pressure-sensing baroreceptors [2,45].

1.3. Arrhythmias

Additionally, the new onset of atrial fibrillation has been repeatedly described during sepsis associated with pneumonia, where an increased production of inflammatory cytokines (including IL-6, IL-8, and tumor necrosis factor α) is considered to contribute to left atrial electric remodeling, which increases the risk of AF [46]. In the long term, it is estimated that up to 50% of patients have recurrent episodes of AF within 1 year of their episode of sepsis [47].

Since the beginning of the SARS-CoV-2 pandemics, several large studies have been conducted, as it quickly became obvious that the acute lung infection has also had an had an impact on multiple organ systems, including the cardiovascular system. Persistent cardiac arrhythmias after SARS-CoV-2 infection have been reported, and the overall prevalence of cardiac arrhythmias ranges from 10 to 20% [48].

Among cardiac arrhythmias, new-onset atrial fibrillation (newAF), defined as a new or first detectable episode of a chaotic and irregular atrial rhythm, whether symptomatic or not, usually confirmed through a 12-lead ECG, is the most frequently encountered arrhythmia in patients affected by infectious diseases, often coexisting with CAP. It has been repeatedly associated with increased mortality in CAP patients, especially in critically ill ones. Because of this, management and the clinical outcome (both short- and long-term) are more complicated than in general terms [37].

Recent data underline the importance of early detection of AF due to its high recurrence risk and related adverse outcomes, surpassing the inaccurate concept that newly detected AF in a specific context, such as pneumonia, was a „benign" form of arrhythmia without clinical implications [46–49]. Recent observational studies' data revealed that between 1% and 11% of hospitalized CAP patients experienced a new or worsening pre-existing arrhythmia [2]. Among 10 studies, the pooled prevalence of new AF was 7.6%, and the incidence of overall cardiac complications was 17.7% [46].

1.4. Myocardial and pericardial disease after CAP

Myocarditis is an inflammatory disease of the cardiac muscle that can be acute or chronic. The acute onset of myocarditis is generally caused by a viral

infection, while chronic myocarditis is usually found in patients with autoimmune disorders.

Respiratory viruses are considered to be the most common triggers of myocarditis. Adenoviruses, enteroviruses, influenza viruses, and coronaviruses are the most frequently encountered ones, but HIV, parvovirus B19, or human herpes virus 6 can also affect the myocardium. The first two above represent the most encountered ones, and they are recognized as primary cardiotropic viruses, directly damaging the myocardial tissue [36,50].

The clinical presentation of viral myocarditis is heterogeneous, and patients may present with chest pain, fatigue, fever, dyspnea, or othopnea, ranging from an asymptomatic disease to decompensated heart failure, cardiogenic shock, and sudden cardiac death. The diagnosis is a challenging one, with the gold standard being encomyocardial biopsy [36].

There is proof that during enteroviral myocarditis, the recovery from the disease, which is shown by complete virus clearance, occurs in only half of subjects, with a poor outcome in the long term if the viral activity persists after the acute episode, but more studies must be conducted in order to prove the direct impact. Among other agents, both Influenza A and B are considered to be cardiotoxic viruses, leading to an activation in immune system responses. During the SARS-CoV-2 infection, there have been cases of myocardial involvement, but more study must be done in order to establish the causal relationship. Cardiac magnetic resonance imaging (MRI) was performed in patients, as the abnormalities can be easier identified and are more prevalent than cardiac biomarkers. Studies revealed that cardiac involvement was found in 78% of subjects, while myocardial inflammation was present in 60% of them [50–53].

The most common pathology that affects the pericadium is represented by pericarditis of viral ethiology, which is the inflammation of the pericardial sac. Pericarditis can also be associated with other pericardial syndromes, such as pericardial effusion without major hemodynamic compromise, cardiac tamponade, constrictive pericarditis, and effusive-constrictive pericarditis. It can be classified according to its duration as acute, subacute, chronic (persisting for more than 3 months), or recurrent (30% of cases). Acute pericarditis is an inflammatory disease produced mainly by viruses and characterized by the infiltration of immune cells into the pericardium. The diagnosis requires the presence of two types of typical pericardial chest pain (worse with inspiration or when lying down and improved by sitting up or forward), specific electrocardiogram (ECG) abnormalities, pericardial effusion, and pericardial friction rub. Most cases resolve within a month, and they can be treated with a non-steroidal anti-inflammatory drug (NSAID) such as Ibuprofen for 1-2 weeks, usually with a proton pump inhibitor and Colchicine [50, 54–57].

Enteroviruses (in 25% of cases), adenoviruses (19% of cases), and influenza virus (6%) are the most commonly encountered viruses in patients with upper respiratory infections who develop pericarditis. When the inflammatory process affects both the pericardum and myocardum muscles, myopericarditis occurs. This syndrome is associated with enteroviral infection in 15% and adenoviral, influenza, or parainfluenza in 10% each [58-59].

3. Conclusions

With an increase in both short- and long-term mortality, the cardiovascular complications that arise after respiratory tract infections have an utmost impact on the outcomes for patients. Patients with severe pneumonia, older age, and cardiovasculcar comorbidities are exposed to developing cardiovascular complications. For these categories, influenza and pneumococcal immunization

should represent a priority, both for patients at risk and for health professionals.

A more precise understanding of the pathophysiological aspects of heart diseases concurrent with pneumonia has been done by distinguishing the events as plaque-related, such as the AMI, or plaque-unrelated, including arrhythmias and heart failure. There still remain unknown mechanisms, for example, about what happens at the virus-cardiomyocyte level. The long-term consequences have not been elucidated yet, and new investigations may lead not only to better risk stratification scales but also to a breakthrough for prophylactic anti-inflammatory and immunosuppressive therapies, which, in a carefully selected group of patients, may reduce morbidity and mortality.

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