# Pneumonia as a Multisystemic Disease

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**KEYWORDS**

• Pneumonia • Systemic • Risk factors • Physiopathology

**KEY POINTS**

- Pneumonia is an infectious disease that affects the lungs but with multisystemic consequences.
- Systemic consequences can occur not only during the acute phase but even in the long term, years after the episode.
- Cardiovascular and neurologic complications are the most frequent and have the greatest impact on patients' health both in the short-term and long-term.

## INTRODUCTION

Pneumonia is a lower respiratory tract infection involving the lungs that also has systemic consequences and distal organ damage. These systemic consequences with multiple organ involvement are frequent during the acute phase mainly in the most severe episodes. Nevertheless, accumulating evidence indicates that these systemic consequences can have an impact or even appear in the long-term. Although pneumonia has traditionally been considered an acute condition, the changes that occur in the host and its inability to return to the previous scenario may have a long-term systemic impact. In fact, mortality in the following year after pneumonia discharge is higher in comparison to not having had pneumonia.

The article examines recent literature on the systemic sequelae following a community-acquired pneumonia (CAP), including SARS-CoV-2 pneumonia, in the short-term and the long-term.

## COMPLICATIONS AND SYSTEMIC CONSEQUENCES OF COVID-19

COVID-19 has impacted millions of people worldwide with significant mortality. After the acute episode, many survivors may experience sequelae and symptoms. There is great heterogeneity in the definition of post-COVID sequelae. Some proposed terms include *post-COVID-19 conditions* (PCCs), *postacute sequelae of SARS-CoV-2 infection* or *long COVID* among others.[1] In October 2021, the World Health Organization defines persistent COVID as *a condition that occurs in individuals with a history of probable or confirmed SARS-CoV-2 infection, usually occurring 3 months after infection with symptoms that persist at least infection with symptoms that persist for at least 2 months and cannot be explained by other diagnoses*.[2]

The development of complications after an infection is not exclusive to SARS-CoV-2. The term *postacute infection syndromes* has

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**Abbreviations**

| | |
|---|---|
| CAP | community-acquired pneumonia |
| CNS | central nervous system |
| ME/CFS | myalgic encephalomyelitis/chronic fatigue syndrome |
| MSCs | mesenchymal stem cells |
| NETs | neutrophil extracellular traps |
| NHPs | nonhuman primates |
| PCCs | post-COVID-19 conditions |
| TLRs | toll-like receptors |

encompassed the set of sequelae that occur after an infection, especially viral.[3] The development of persistent symptoms such as fatigue, pain, weakness, depression, or sleep disturbance has already been described in relation to the 2003 (SARS-CoV-1) and 2021 (MERS) coronavirus epidemics.[4,5]

## *Epidemiology and Risk Factors*

The long-term systemic consequences of COVID-19 are highly diverse and encompass multiple organs and systems (**Fig. 1**). The prevalence of complications and sequelae is highly variable and it ranges from 10% to 70%. In a meta-analysis involving 120.970 individuals who had undergone SARS-CoV-2 infection, the incidence of long COVID was 56.9%. The most frequent manifestations were general ones (31.0%) (ie, fatigue), and respiratory (24.5%) (ie, dyspnea). Neurologic (19.7%), psychiatric (20.3%), and cardiac (11.0%) manifestations were also relevant.[6] There is little information on the duration of these symptoms and sequelae, which in some cases may persist at least beyond 1 to 2 years after infection.[7–9]

Multiple risk factors have been identified related to the presence of long COVID but in some cases the information is controversial. These risk factors include age, sex, socioeconomic factors, comorbidity, vaccination status, the severity of the acute phase, or even reinfection by SARS-CoV-2.[1,10–12] Obesity and lipid metabolism disorders may act as promoters and facilitators of inflammation and endothelial dysfunction aggravating acute illness and the risk of long COVID.[10,13] In addition to relating severity in the acute phase, Turner and colleagues identified the initial symptoms (fatigue, headache, dyspnea, and arthromyalgia) that are subsequently related to the development of long COVID.[11] However, in the previously mentioned meta-analysis there was insufficient evidence to relate the severity of acute illness to the occurrence of sequelae.[6] There are also studies that relate female sex with long COVID, despite the fact that the highest acute morbidity and mortality were related to males.[1,11] Separating by groups, the most frequent symptoms in women are general, neurologic, and cardiovascular symptoms, while in the elderly they are general, psychiatric, respiratory, digestive, and skin symptoms.[6]

## *Physiopathology*

The wide variability of manifestations in COVID-19 survivors, with multisystem involvement, suggests different underlying pathophysiological mechanisms. Broadly, sequelae can be explained by 6 different hypothesis: viral persistence, immune dysregulation, microbiome dysbiosis, endothelial inflammation, neuronal inflammation, mitochondrial dysfunction, and direct damage.[14]

- Viral persistence: After resolution of the infection, virus can still be detected in the organism because it persists as a reservoir in different tissues.[15] This viral persistence favors

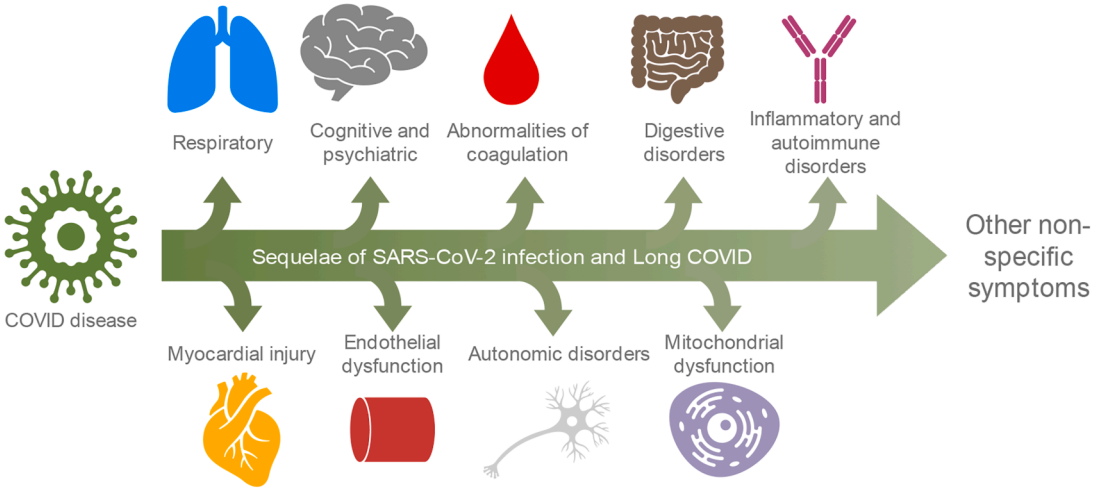



**Fig. 1.** Main long-term systemic consequences of COVID-19.

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constant immune activation. On the other hand, the effect on the immune response favors the reactivation of latent viruses, such as herpesviruses, which contribute to the persistence and appearance of symptoms.

- Immune dysregulation: SARS-CoV-2 causes dysregulation of the immune response toward a proinflammatory state. This effect is favored by the loss of regulatory T lymphocytes in the context of lymphopenia and favors autoimmune mechanisms.[16]
- Microbiome dysbiosis: It has been described that SARS-CoV-2 can act as an intestinal microbiota bacteriophage, which acts as a reservoir and on which it induces the proliferation of certain bacteria causing intestinal dysbiosis.[17]
- Endothelial inflammation: Alteration of the vascular endothelium plays a central role in inflammation and hemostasis by acting as a regulator of both pathways. At the same time, endothelium can suffer damage as a consequence of inflammation and thrombotic phenomena. Both pathways are also related, such that the inflammatory response favors thrombotic phenomena and the alteration of coagulation induces increased expression of adhesion molecules and proinflammatory cytokines in the vascular endothelium. In addition, changes in thrombus formation have been detected in individuals with SARS-CoV-2, which confers increased fibrinolytic resistance and it is associated with proinflammatory prothrombin molecules.[11] In summary, SARS-CoV-2 causes endothelial dysfunction, thrombotic and proinflammatory mechanisms, which may contribute to the development of sequelae.
- Neuronal inflammation: COVID-19 can cause neurologic damage through several mechanisms secondary to systemic inflammation and viral load.[18] The most important ones include microglia dysfunction, neurovascular inflammation with damage to the blood-brain barrier, metabolic dysfunction in the central nervous system, and myelin injury among others.
- Mitochondrial dysfunction: Long COVID symptoms like chronic fatigue, dyspnea, and cognitive or cardiac alterations are often difficult to explain. During the acute phase, the virus exploits mitochondria for replication, potentially causing structural and functional damage, similar to other postinfectious syndromes such as myalgic encephalomyelitis/chronic fatigue syndrome ME/CFS.[19] Mitochondrial dysfunction affects metabolism, ATP production, oxidative stress, and inflammatory responses.[20–22] Reduced energy production explains chronic fatigue, dyspnea, exercise intolerance, and cognitive impairments, while metabolic alterations contribute to exercise intolerance, weight changes, and nutritional deficiencies. Increased oxidative stress and inflammatory mechanisms exacerbate chronic conditions overlapping with long COVID manifestations. Mitochondrial dysfunction may also impair vascular endothelial function, influencing blood pressure variations, and causing dizziness and other sequelae.[23] Molnar and colleagues evaluated mitochondrial function and oxidative stress biomarkers in long COVID patients. Findings supported the link between mitochondrial dysfunction and long COVID, identifying specific symptoms associated with individual biomarkers, such as dizziness linked to peroxiredoxin-2, suggesting diverse mitochondrial processes underlie the condition.[24]
- Direct damage: Finally, SARS-CoV-2 causes injury to various tissues and organs. It can be attributed to its direct action but also secondarily to its action as tissue hypoxia resulting from lung damage and thrombotic phenomena.[25]

### *Respiratory sequelae: from radiological and functional alterations to symptoms*

SARS-CoV-2 infection has primarily respiratory consequences with long-term clinical sequelae, especially suffering dyspnea and cough.[26] The persistence of respiratory symptoms during the first 3 months ranges from 40% to 94% and progressively decreases to 35% to 45% during the follow-up.

Similarly, radiological and functional alterations (established as $DL_{CO}$) at 6 months vary between 38% to 66% and 47% to 55%, respectively, with progressive improvement to 25% to 28% and 20% to 31% at 1 year.[27–29] However, clinical manifestations do not always reflect structural or functional respiratory damage. For example, the RECOVID study revealed that 43% of individuals with symptoms at 12 months showed complete radiological and functional resolution, while 46% of asymptomatic individuals presented with radiological and/or functional sequelae.[28]

Factors associated with each sequelae differ based on age, sex, and comorbidities,[28] except for infection severity (assessed by prognostic scales or the need for respiratory/ICU support), which has been linked to all 3 types of sequelae. The COVID-FIBROTIC registry, analyzing fibrogenesis and its relationship with sequelae development, identified associations with specific biomarkers.[29]

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### *Myocardial injury*

Cardiovascular symptoms are frequent during both the acute and convalescent phases of COVID-19. The ACE2 receptor in the myocardium may facilitate direct viral cell damage during the acute phase and contribute to RAAS dysregulation. Hypoxemia and a prothrombotic microvascular state also contribute to myocardial injury via hypoxia. Additionally, inflammatory alterations during and after the acute phase exacerbates thrombotic phenomena and promote tissue damage and fibrotic repair, leading to myocardial stiffness, contractile dysfunction, and arrhythmias. Autoantibody formation may further contribute to myocardial dysfunction.[10]

### *Neurologic sequelae: cognitive symptoms and autonomic dysfunction*

Nearly half of COVID-19 survivors may experience neurocognitive dysfunction 1 year later.[7] Kanberg and colleagues analyzed the pathophysiological mechanisms of long COVID. In an initial 2021 study, biomarkers of central nervous system (CNS) injury were evaluated in COVID-19 patients. Initially elevated, these biomarkers normalized over time, regardless of symptom persistence, suggesting post-COVID neurologic sequelae are not linked to ongoing CNS damage.[30] A second study comparing patients with and without post-COVID neurocognitive symptoms (PCC), found no evidence of viral persistence or immune response differences in the CNS, indicating that PCC likely results from events during the acute phase.[31]

Symptoms such as palpitations, orthostatic intolerance, dizziness, exercise intolerance, or nausea are consistent with autonomic dysfunction syndromes like postural orthostatic tachycardia syndrome and orthostatic hypotension, previously observed after other infections.[32] Peripheral vascular tone alterations due to dysautonomia cause relative hypovolemia, resulting in these manifestations. Cerebral hypoperfusion, direct viral neurologic damage, and autoantibody-induced C and A fiber neuropathy may explain dysautonomia following COVID-19.[11,33–35] Vagus nerve involvement, either through direct viral action or inflammation, may also contribute to autonomic symptoms, as well as gastrointestinal, phonatory, or swallowing sequelae.[36]

## COMPLICATIONS AND SYSTEMIC CONSEQUENCES OF COMMUNITY-ACQUIRED PNEUMONIA

With the emergence of SARS-COV-2, greater awareness has been raised about the systemic implications of respiratory infections. However, this fact was already widely known in CAP.[37] Cardiovascular complications, neurologic problems, and muscular dysfunction are the most well-known and studied systemic problems in CAP (**Box 1**).

## CARDIOVASCULAR COMPLICATIONS

### *Epidemiology and Risk Factors*

The relation between cardiovascular system and infections has been recognized during and after the acute episode.[38–41] That association was demonstrated up to 10 years in CAP hospitalized patients discharged alive when compared to patients with similar age and comorbidities but not hospitalized due to pneumonia.[42] Notably, the negative impact on cardiovascular (CV) system may appear in patients without prior heart diseases. All the accumulated evidence has led to pneumonia being considered a cardiovascular risk factor.[43–46]

The frequency and timing of CV complications differs among the different studies due to methodological variations, definitions, and population. Thus, CV events are more common in the most severe episodes but not negligible in the outpatients. CV are more frequent during the first days of the acute episode, but its frequency in the subsequent year of follow-up was up 10% and up 34.8% within 10 years.[42,47] The incidence of each type of cardiovascular event is also variable. In a meta-analysis published by Corrales-Medina and colleagues,[48] the incidence reported for each cardiovascular event (CVE) was—heart failure (14%, range 7%–

**Box 1**
**Main long-term systemic consequences in community-acquired pneumonia**

- Long-term systemic consequences of pneumonia
  - Cardiovascular
    - Arrhythmia
    - Heart failure
    - Myocardial infarction
    - Atherosclerosis progression
    - Venous thromboembolic disease
  - Neurologic
    - Dementia
    - Cognitive decline
  - Muscle
    - Muscle dysfunction
    - Chronic fatigue syndrome

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33%), arrhythmia (5%, range 1%–11%), and acute coronary syndrome (5%, range 1%–11%). Another study by Tralhao and colleagues reported 13.9% of overall cardiac complications with 4.5% of acute coronary syndromes, 9.2% of heart failure, 7.2% of arrhythmias, and 0.71% of stroke.[49]

In CAP patients who develop in-hospital CV complications mortality is not only higher during the acute episode but also in the long-term.[50–52] Aldas and colleagues, found that CVE was an independent factor related to early (first 30 days) and late (1 year) mortality, with a 16% of 1-year mortality attributed to cardiovascular disease.[53] In another study by Violi and colleagues,[54] CV complications were associated with a 5-fold increase in 30-day mortality.

The occurrence of CV complications was more frequent depending on host characteristics and age, initial severity of the episode and causal microorganisms.[40,55,56] Adults with prior cardiac risk factors, hypertension, chronic obstructive pulmonary disease or renal chronic diseases, and elderly patients were at higher risk.[52–54] Initial severity, the presence of sepsis, ICU admission requirement also increased the risk. However, even mild respiratory infection is associated with an increased risk of myocardial infarction for several months after the onset of infection.[41]

### *Pathophysiology*

There are several mechanisms altered during the acute phase that may affect CV system pointing out a multifactorial cause (Fig. 2).[41,43,57] During pneumonia, the impaired gas exchange provoke hypoxemia and vasoconstriction reducing oxygen supply to vital organs that may enhance vulnerability to ischemic events. Systemic inflammation with the increases in proinflammatory cytokines can increase inflammatory activity triggering several other alterations and provoking instability within coronary atherosclerotic plaques, making them prone to rupture. During pneumonia there is a prothrombotic state, the coagulation cascade is activated by cells of the innate immune system, such as neutrophils and monocytes, resulting in clot formation mainly in the microcirculation, a process known as immunothrombosis.[58] In fact, excessive neutrophil recruitment and neutrophil extracellular traps (NETs) formation can provoke endothelial activation, contributing to local immunothrombosis and leading to organ damage and failure. Platelet activation also contribute with the prothrombotic state due to several pathways: inflammation, NETs and pathogens themselves. In fact, platelets express numerous immunoreceptors that enable them to recognize intravascular pathogens, including toll-like receptors (TLR), which bind their respective pathogen-associated molecular patterns and damage-associated molecular patterns.[59] Platelet TLR-2 can directly bind the antigens of *Streptococcus pneumoniae*, which leads to platelet activation. Endothelial dysfunction and microthrombotic complications can rapidly lead to multiple organ dysfunction. Inflammation, altered immune system, and organ damage may

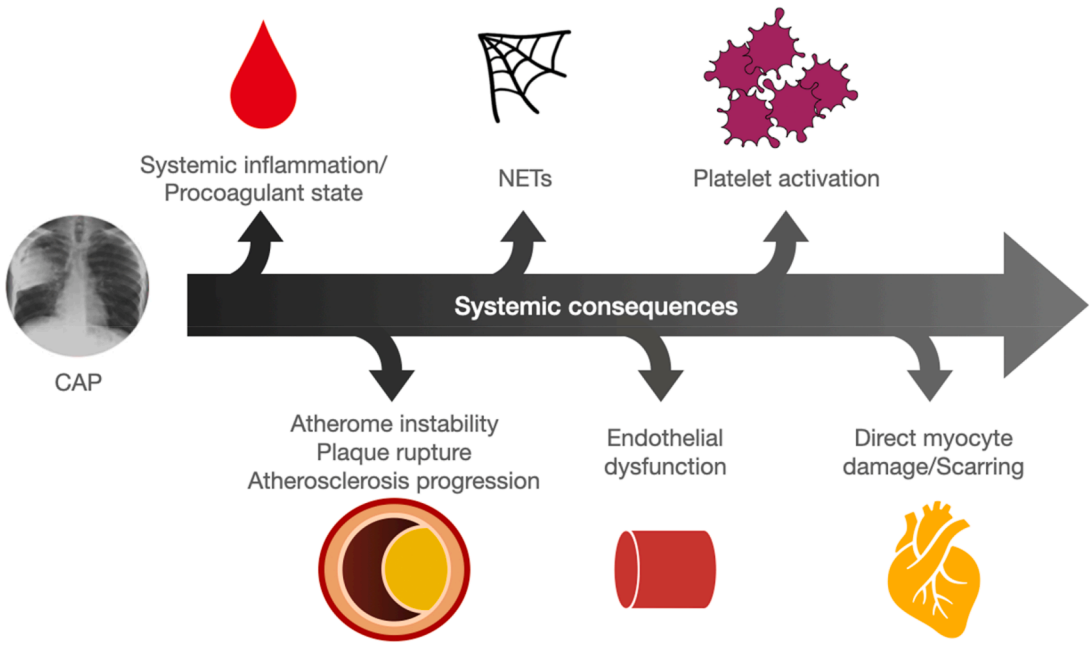



**Fig. 2.** Pathophysiological mechanisms of cardiovascular consequences in community-acquired pneumonia.

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persist beyond the acute phase of infection as reported in some studies.[47,60] Besides, some mechanisms and mainly inflammation may contribute with atheromatous progression.[61,62]

Nonhuman primates (NHPs) pneumonia models have revealed that invasive pneumococcal disease leads to translocation of the pneumococcus into the myocardium resulting necroptosis and apoptosis were detected in the myocardium of both acutely ill and convalescent NHPs. Evidence of cardiac scar formation was observed explaining CV long-term consequences.[63,64] In addition, Alhamdi and colleagues have reported that circulating pneumolysin directly induced cardiac injury.[65] Recently, a persistent antigenemia release from remnants of capsular polysaccharides in resident tissue macrophages and other cell types has been suggested as another potential mechanism for long-term CV events.[57] In a murine model with intratracheal administration of lipopolysaccharide, Jaw and colleagues showed that circulating neutrophils contribute to acute destabilization and rupture of atheroma plaques.[61]

### *Management and prevention*

Cangemi and colleagues reported that treatment with corticosteroids reduced cardiac complications possibly due to the decrease in systemic cytokine production and inflammation.[66,67] Treatments directed to reduce thromboinflammation in CAP (ie, ticagrelor, statins, or aspirin) have showed an improvement in outcomes opening a new avenue for interventional studies aimed to decrease CVE and mortality.[68–70]

Alongside, measures to prevent pneumonia though vaccination have demonstrated a decreased of risk for CV complications, especially in elderly. That benefit is due not only for the reduction of episodes and severity of pneumonia. It has been suggested that vaccines may modify the immune-inflammatory model of atherogenesis.[71,72]

## NEUROLOGIC COMPLICATIONS

### *Epidemiology and Risk Factors*

Among the potential complications associated with pneumonia are neurologic complications. In recent years, various studies have demonstrated this relationship, nevertheless, it remains a neglected issue that demands further investigation.[73] This relationship has been shown to be bidirectional since the presence of cognitive impairment increases the risk of pneumonia and vice versa.[74] Neurologic complications related to pneumonia may appear not only during the acute episode but also in the long-term impact. During the acute phase, the most frequent neurologic complication is delirium, an acute disturbance in attention and cognition that may fluctuate over time. It is estimated that around 30% of patients hospitalized for CAP present some symptoms of delirium during their hospital stay, although this figure may vary depending on the severity of the condition.[75] On the other hand, patients who survive pneumonia are at risk of developing neurologic complications in the long-term. The most frequent and studied complications are cognitive impairment or dementia.[76,77] In a population-based matched cohort study from the United Kingdom, the incidence rates of cognitive impairment and dementia were 18 per 1000 person-years among persons previously hospitalized with pneumonia versus 13.2 in a matched control cohort.[76] This incidence varies with age, but the risk already exists at an early age, as demonstrated by studies that include patients from 18 years of age onwards.[76,78]

The main known risk factors for cognitive decline and dementia after CAP are (1) aging and the presence of comorbidities, (2) the development of delirium during hospitalization, and (iii) the severity of pneumonia. (1) Older patients and those with comorbidity are more vulnerable to developing cognitive impairment and dementia after pneumonia[76,79,80]; (2) Up to 70% of patients requiring ICU admission develop long-term cognitive impairment.[81,82] Different phenotypes of delirium have been identified depending on the etiology and cause, which may have implications for clinical practice.[81] Delirium may translate the presence of acute neurologic damage that can have a long-term impact.[83] (3) Finally, patients with severe pneumonia requiring mechanical ventilation and/or admitted to the ICU are exposed to greater stress and neurologic damage that increases the risk of developing long-term consequences.

### *Physiopathology*

There are several hypotheses that attempt to explain neurologic damage in pneumonia. These hypotheses focus mainly on the role of systemic inflammation and neuroinflammation, the microbiome, and direct neurologic damage by microorganisms. In many cases, these pathophysiological mechanisms interplay with each other.

Previous studies have shown that low-grade systemic inflammation promotes neurodegeneration. Aging and comorbidities, common factors in patients with pneumonia, promote the presence of chronic systemic inflammation.[84,85] In the case of pneumonia, there is a *high-grade* systemic inflammation and oxidative stress during the acute phase, but it can even persist over time, although

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at a lower intensity.[86,87] This systemic inflammatory stress can cause microvascular and blood–brain barrier dysfunction, and neuroinflammation in the CNS. Ultimately, this may alter the fragile balance maintained by microglia and astroglia.[88–94] Neuroinflammation may also be secondary to an alteration of the microbiome. The lung and gut microbiota interplay each other and may impact on respiratory diseases.[95] At the same time, there is also a symbiosis, and a bidirectional and dynamic cooperation at the immune and metabolic level through the gut microbiota-brain axis.[96] Therefore, there is a complex and fragile axis, the gut-lung-brain axis, which remains virtually unexplored and potentially hides many of the answers to the long-term neurologic consequences of pneumonia.[97] Another possible cause of neurologic alterations and potentially related to the microbiome is direct damage by endogenous bacteria. Several animal models have shown that during severe sepsis or pneumonia, endogenous bacteria can be translocated to the CNS, promoting neuroinflammation and neuronal damage.[98,99] Finally, postmortem studies have shown that sepsis is associated with a specific transcriptional response in the human brain.[100] Its implications remain to be elucidated.

## MUSCLE COMPLICATIONS

The current literature offers limited information regarding muscle complications following an episode of CAP. Although more extensive data exist on muscle failure in sepsis, pneumonia is the most common infection that causes sepsis and more than one-third of hospitalized CAP develop sepsis.[101] In sepsis, a pathologic remodeling of muscle fibers—called muscle dysfunction—has been documented.[102,103] In fact, respiratory muscle failure is one of the leading causes of mortality in patients with sepsis and/or septic shock. In animal studies, several mechanisms have been identified as the origin of muscle failure in sepsis, such as hemodynamic features, cytokines, endotoxins and oxidative stress, among other factors.[104] A recent murine study indicates that the progressive accumulation of mitochondrial abnormalities is the primary driver of postsepsis skeletal muscle weakness. Pharmacologic interventions aimed at preserving mitochondrial function during acute sepsis represent a promising clinical strategy to mitigate postsepsis muscle impairment.[105] Other studies in murine models have shown that postsepsis muscle regeneration is impaired, but treatment with mesenchymal stem cells (MSCs) can reverse this dysfunction. MSCs therapy improves muscle recovery, reduces necrosis and fibrosis, and enhances muscle strength.[106]

Studies in humans with sepsis have observed that carbonylation levels were significantly higher in limb muscles in patients with severe sepsis compared to controls. Nevertheless, no statistically significant differences were observed in respiratory muscles.[107]

ME/CFS is a disabling and debilitating chronic disorder of unknown etiology, officially recognized by the World Health Organization. While the clinical manifestations of ME/CFS are well-defined within established diagnostic criteria, its diagnosis remains one of exclusion, requiring the elimination of alternative medical conditions before confirmation.[108] In CAP, postinfectious CFS has been observed, occurring not only due to viral pathogens but also, notably, as a consequence of bacterial infections, particularly *Klebsiella pneumoniae*, *S pneumoniae*, and *Haemophilus influenzae*.[109]

## SUMMARY

In conclusion, pneumonia is no longer considered only an acute localized respiratory disease because it has systemic implications with potential long-term consequences. Understanding these sequelae is crucial for improving postinfection management and reducing morbidity in affected individuals.

## CLINICS CARE POINTS

- It is necessary to identify early those patients with pneumonia at risk of developing systemic complications.
- The pathophysiological mechanisms underlying systemic complications remain poorly understood.

## DISCLOSURE

The authors have no conflicts of interest.

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