

Community-Acquired Pneumonia Pathogenesis in Patients with Chronic Obstructive Pulmonary Disease

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DOI: 10.18297/jri/vol3/iss2/4

Submitted Date: November 18, 2019

Accepted Date: November 18, 2019

Website: <https://ir.library.louisville.edu/jri>

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Recommended Citation: Ramirez, Julio A and Cavallazzi, Rodrigo. (2019) "Community-Acquired Pneumonia Pathogenesis in Patients with Chronic Obstructive Pulmonary Disease," *The University of Louisville Journal of Respiratory Infections*: Vol. 3 : Iss. 2 , Article 4.

Introduction

Patients with chronic obstructive pulmonary disease (COPD) are at high risk of developing community-acquired pneumonia (CAP). We recently completed a secondary analysis of the University of Louisville Pneumonia Study [1] and documented an annual incidence of 9,369 patients with CAP per 100,000 COPD population [2]. We estimated that 506,953 adults with COPD are hospitalized due to CAP in the United States every year [2]. This incidence rate is almost 18-fold greater than the incidence rate of CAP patients without COPD [2].

Three interrelated factors play a role in the pathogenesis of CAP in COPD patients: 1) abnormalities in the lung microbiome, 2) abnormalities in the lung immunity, and 3) the virulence of the pathogen causing CAP (**Figure 1**). In this opinion piece we would like to speculate that alterations of the lung microbiome may be a critical factor in the increased susceptibility of CAP in COPD patients.

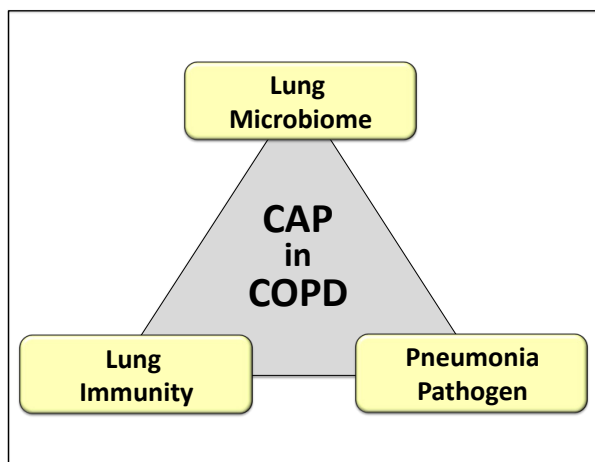


Figure 1 Interplay of lung microbiome, lung immunity and pneumonia pathogen in the pathogenesis of CAP in COPD.

Lung Microbiome

The differences in the lung microbiome from a normal lung to a lung of a patient with COPD are depicted in **Figure 2**. In the normal lung, the alveolar microbiome contains a low number of organisms with a high diversity of bacterial communities (**Figure 2A**). The microbiome in the normal lung is constituted primarily of anaerobic organisms, with predominance of the phylum Bacteroidetes [3]. Some microorganisms are living freely in the alveolar space, in a planktonic form, but half of the bacterial communities are attached to alveolar cells [4]. The alveolar flora may impede the multiplication of new arriving pathogenic bacteria by several mechanisms. A normal microbiome may compete for attachment sites on alveolar cells, may compete for essential bacterial nutrients, or may produce antibacterial substances to inhibit the growth of pathogenic bacteria.


In the COPD patient there are alterations in the number and types of organisms present in the lung microbiome, a phenomenon known as dysbiosis [5]. In the COPD lung the microbiome contains high number of microorganisms, with a low diversity of bacterial communities. It is likely that several of these organisms are living in cell-associated biofilm communities (**Figure 2B**). The abnormal alveolar microbiome of COPD patients may be unable to impede the multiplication of invading pathogens, enhancing susceptibility to pneumonia.

Lung Immunity

Macrophages, surfactant, and oxygen levels play a role in alveolar immunity. Alveolar macrophage phagocytosis of new organisms arriving to the alveoli is a primary step in the prevention of pneumonia [6]. Surfactant acts as a component of the alveolar host defenses by binding to the surface of pathogens arriving to the alveoli [7]. Opsonization of bacteria by surfactant facilitates phagocytosis by alveolar macrophages. Normal

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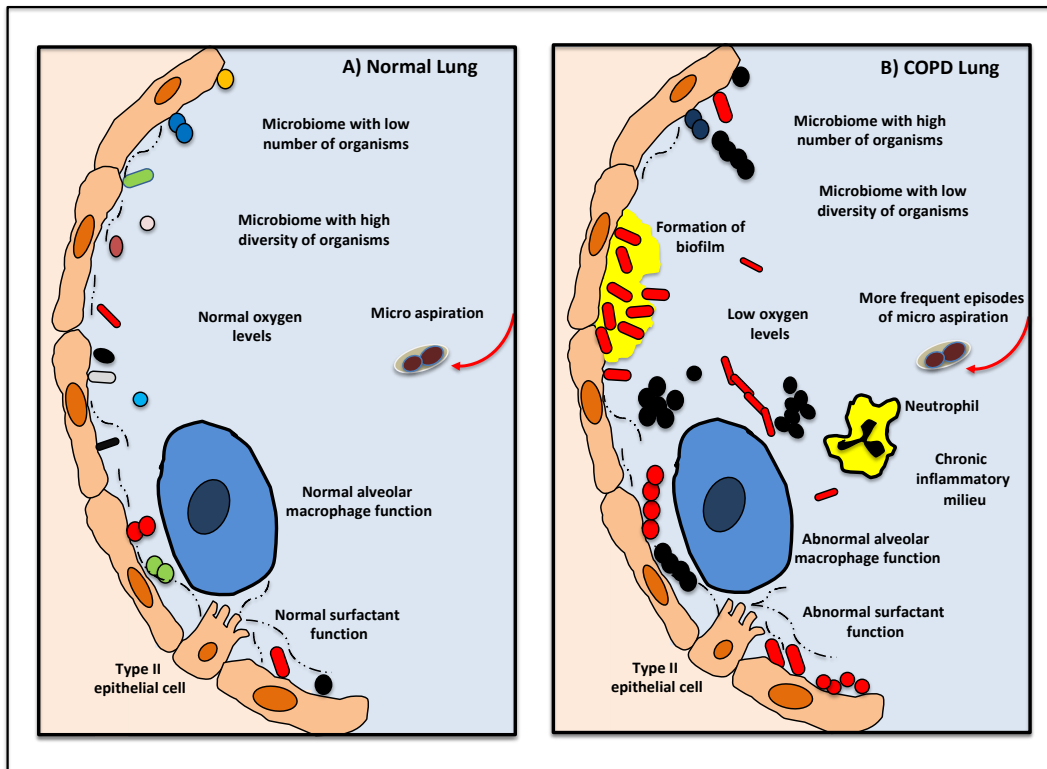


Figure 2 Characteristics of lung microbiome in a normal lung (A) and a COPD lung (B).

oxygen level is important in alveolar immunity since hypoxemia is associated to local inflammation and immune dysfunction [8]. Alveolar dysbiosis in COPD patients may enhance susceptibility to pneumonia by producing abnormal macrophage function, surfactant degradation and low oxygen levels.

Pneumonia Pathogen

As the severity of COPD progresses over time, the risk for the patient to develop CAP increases, and the number of pathogens able to cause CAP expand (**Figure 3**). The patient with mild to moderate COPD will be at risk of infection with the pathogens causing CAP in non-COPD patients with the addition of beta-lactamase producing bacteria such as *Haemophilus influenzae*, *Moraxella catarrhalis*, and *Staphylococcus aureus*. In patients with severe COPD the list of likely organisms able to cause CAP will extend to Gram-negative Enterobacteriaceae

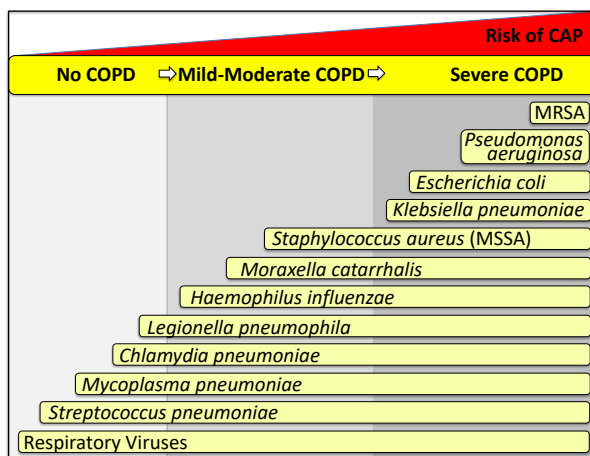


Figure 3 Likely pathogens causing CAP in COPD patients according to severity of COPD.

such as *Klebsiella pneumoniae* or *Escherichia coli* as well as Gram-negative non-fermenting bacilli such as *Pseudomonas aeruginosa* [2,9]. According to the local epidemiology, methicillin-resistant *Staphylococcus aureus* (MRSA) may also cause CAP in patients with severe COPD.

CAP Pathogenesis

The primary model of pneumonia pathogenesis in COPD patients will start with the pneumonia pathogens arriving to the alveoli in greater number due to more frequent episodes of microaspiration. Once in the alveoli the pneumonia pathogens will overcome the abnormal alveolar microbiota as well as the abnormal alveolar immunity. The uncontrolled multiplication of the pathogen will cause the development of pneumonia.

Another possible model of pathogenesis of CAP in COPD patients may include a combination of alveolar multiplication of new pathogenic bacteria arriving to the alveoli associated to uncontrolled multiplication of some of the species present in the alveolar microbiota. In this type of pathogenesis, the etiology of pneumonia will be polymicrobial, with a combination of invading pathogenic bacteria plus bacteria normally present in the alveoli.

A final model of pathogenesis may involve the uncontrolled multiplication of some of the bacteria already present in the alveolar microbiota. In this case, the etiologic agent of pneumonia will be bacteria that typically constitute the alveoli normal flora. This scenario may explain why in several COPD patients with CAP an etiologic agent is not identified, since alveolar microbiome bacteria cannot be isolated using regular culture techniques.

Conclusion

The alveolar microbiome plays an important role in maintaining a normal alveolar immunity. In patients with COPD, the dysbiosis of alveolar microbiota may alter several elements of alveolar immunity. In this opinion piece we speculate that alveolar dysbiosis may be a primary reason for the increased susceptibility to CAP in COPD patients.

Funding Source

The authors received no specific funding for this work.

Conflict of Interest

No authors have conflicts of interest to report.

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