A Continuum of Disease from Community-Acquired Pneumonia to Multiple Organ Dysfunction Syndrome

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DOI: 10.18297/jri/vol2/iss2/1/

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Introduction

Community-acquired pneumonia (CAP) is one of the primary causes of sepsis, septic shock, acute respiratory distress syndrome (ARDS), and multiple organ dysfunction syndrome (MODS) [1-3]. The chain of immune responses in patients with pneumonia can be considered as a continuum of disease from an initial appropriate response in patients with CAP, to a deleterious response that encompasses Severe CAP, Sepsis, Septic Shock, ARDS and MODS. As the lung infection overwhelms the natural defenses that are produced by physiologic pulmonary and systemic inflammation, a deeper line of defense is necessary. At this point, the immune system may develop an inflammatory response that may be damaging to vital organs, culminating with organ failure. In this opinion piece I will review the pathophysiology of CAP and construct a continuum of disease from CAP to MODS.

Pathophysiology of CAP

In a prior opinion piece in the Journal of Respiratory Infections, I stated that the pathogenesis of CAP is evolving as we recognize that the lower respiratory tract is not sterile as we previously considered [4]. A schematic representation of the alveolar space, containing the alveolar macrophage as well as the normal alveolar flora, is depicted in **Figure 1**. The concept that organisms should first arrive to the alveoli as the first step in the pathogenesis of CAP may not be necessary in all patients. Multiplication of bacteria or viruses already present in the alveoli, as part of the normal flora, may be an important etiology of CAP. The traditional typical and atypical pathogens able to cause CAP are not considered as part of the normal alveolar flora. For these organisms, the first step in the pathogenesis of CAP is their arrival to the alveolar space primarily via microaspiration of oropharyngeal secretions (**Figure 2**).

Figure 1. A schematic representation of the alveolar space, containing the alveolar macrophage as well as the normal alveolar flora.

Figure 2. Arrival of *S. pneumoniae* to the alveolar space via microaspiration of oropharyngeal secretions.

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Figure 3. Alveolar macrophage phagocytosis of *S. pneumoniae* and production of cytokines and chemokines.

Figure 4. Alveolar macrophage phagocytosis of *S. pneumoniae* and production of cytokines and chemokines.

Figure 5. The physiologic host local and systemic response characterize patients with mild to moderate CAP.

Figure 6. The host dysregulated inflammatory response indicates that the patient develops sepsis. At this point the patient is considered to have Severe CAP.

The alveolar macrophages are professional phagocytes that represent an important defense mechanism against multiplication of organisms at the alveolar level. The normal alveolar flora may have a defensive role against respiratory pathogens. If these defense mechanisms fail to contain the local multiplication of organisms, the macrophage will produce a series of cytokines to bring new phagocytes to the alveolar space (**Figure 3**). Alveolar epithelia cells are likely involved in the production of local cytokines in the context of pneumonia. Local production of cytokines will generate an inflammatory response with increased local microvascular permeability. This will facilitate the movement of neutrophils, lymphocytes, dendritic cells, red blood cells, platelets, proteins, and fluid into the alveolar space. The presence of this alveolar exudate will aid the macrophages in the killing of alveolar pathogens. This process characterizes the initial pulmonary inflammatory response or local inflammatory response (**Figure 4**).

As a consequence of the local production of cytokines and chemokines, these mediators will spill into the systemic circulation and serve as a way for the lung to communicate with a series of organs such as the liver, bone marrow, brain, and spleen. During these interactions, the lung will submit and receive inputs and generate an integrated systemic inflammatory response. The liver will produce an acute phase response, characterized primarily by hepatocyte production of

C-reactive protein. The bone marrow will produce neutrophils and other cells necessary to migrate into the alveolar space. The brain thermoregulatory center will elevate the body temperature. The spleen will produce the appropriate immunoglobulins according to the antigenic characteristics of the pulmonary pathogen. All of this lung orchestrated local and systemic inflammatory responses are considered a normal host physiologic response to the growth of pathogenic organisms in the alveolar space (**Figure 5**). The physiologic abnormalities produced by the local and systemic host inflammatory response will explain most of the clinical and laboratory abnormalities in patients with pneumonia.

Pathophysiology of CAP with Sepsis

In some patients the initial physiologic systemic inflammatory response can become dysregulated. This abnormal response will be associated with tissue injury and organ dysfunction. The progression from a physiologic to a dysregulated systemic inflammatory response indicates that pneumonia is now complicated with sepsis [5]. When a patient with CAP develops sepsis, the patient will have a more severe clinical picture. From a pathogenesis point of view, it can be considered that when a patient with CAP advances to sepsis, then the patient has severe CAP (**Figure 6**).

Figure 7. Progression of the dysregulated inflammatory response will present clinically as a patient with severe CAP plus septic shock, and/or ARDS, culminating with MODS.

Pathophysiology of CAP with Septic Shock, ARDS, and MODS

In some patients with CAP, the levels of inflammatory mediators that are produced with the intention to damage the pathogenic organisms in the lung, produce significant tissue damage. This may represent a tradeoff of the immune response in patients with persistent microbial challenge. Dysfunction of the cardiovascular system will manifest as hypotension and septic shock. Dysfunction of the pulmonary parenchyma beyond the area of CAP will manifest as ARDS. Progression to dysfunction of multiple other organs and systems will manifest as MODS (Figure 7).

Conclusions

In this opinion piece I categorized patients with CAP as a continuum of disease using a pathophysiologic approach. Patients with CAP of mild or moderate severity have an

appropriate pulmonary and systemic inflammatory response. If this physiologic response failed to control the pulmonary infection, the immune system compromises. On one hand, the immune system produces an exaggerated inflammatory response in an attempt to control the pulmonary infection, on the other hand, the same inflammatory response will produce organ dysfunction. At this point the patient will have a clinical picture of severe CAP and will have evidence of sepsis. Patients with CAP and a persistent dysregulated inflammatory response may develop septic shock, ARDS, or MODS. Categorizing the severity of CAP using a pathophysiologic approach may help us to better study new treatment strategies.

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