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EDITORIAL

The lung microbiome and pneumonia: Where precision medicine meets pulmonology

Human wellbeing is the result of dynamic networking between five nodes: mind–brain, genes, epigenetics, environment, and microbiome.[1] These nodes communicate with each other through messengers, including neuroendocrine peptides and microbial metabolites. One can imagine this grand system as a symphony orchestra except without a permanent conductor. To hear a well-tuned and performed symphony, a healthy state, the function of each node is synchronized with the other four. The disorder is the phenotype of any disturbance in the network.

So far, mostly our attention spectrum to study, prevent, and treat each disorder(s), has been narrowed to a limited cause and effect or association between an agent and the affected organ. When it comes to multisystem disorders like multiple system organ failures in a septic patient with pneumonia, our capability to prevent, predict and treat the patient is as good as the best survival rate for septic shock.

In this narrative review article, using the above-proposed model to study a disease, our new understanding of the pathogenesis of pneumonia and its potential implications for prevention, treatment, and policy-making are discussed.

The classic theory of the pathogenesis of pneumonia[2] assumes that the lung is a sterile organ, and the etiologic microorganism enters, colonizes, and invades pure airways and pulmonary parenchyma either through aspiration from the digestive tract or circulation. Advances in genetics techniques to detect microbes, like 16S rRNA gene sequencing[3] and metagenomics, have shown that the lung is not a sterile organ as we previously assumed. Indeed, a constellation of different microorganisms lives in small airways and alveoli. Compared with the gut microbiome, however, the density and diversity of the lung microbiome are limited. The lung was considered a sterile organ because the routine sputum cultures fail to detect anaerobic microorganisms.[4]

In healthy lungs, Proteobacteria, Firmicutes, and Bacteroidetes are the most commonly identified bacteria, while, Streptococcus, Prevotella, Fusobacteria, and Veillonella predominate, with potential pathogens, such as Haemophilus and Neisseria, are a smaller fraction of a healthy lung microbiome. Interestingly, the same bacterial population is the normal flora of the mouth in healthy individuals.[5] The formation and diversity of the pulmonary microbiome (PM) start with the exposure of newborn oral mucosa to maternal vaginal flora with subsequent microaspiration of the newly formed oral flora into the airways and alveolar epithelial cells. Microaspiration is the primary source of populating PM, inhalation and intestinal microbiome are other sources. Intestinal microbiome influences PM directly by the migration of microorganisms to PM via the lymphatic system, and indirectly, by immune modulation. Submucosal lymphocytes, dendritic cells, and macrophages exchange information with the intraluminal microbiome. These interactions set the immune tone and affect the function of immune cells in response to newly invading pathogens. Migrating immune cells from the intestine to bronchial submucosa and lung interstitial space by lymphatic flow, modulate the pulmonary defenses and susceptibility to virulent pathogens. Altered intestinal microbiome after broad-spectrum antibiotic therapy or intestinal ischemia in acute illness can increase the risk of developing pneumonia or ARDS.[6]

The content and diversity of the pulmonary microbiome at any given time depends on dynamic interactions between immigration, colonization, and elimination processes. Through aging, the diversity of the PM evolves and adapts to the living environment, diet, and submucosal immune tone, among other factors. For example, a high fiber diet by producing more short-chain fatty acids (SCFA) enhances Bacteroides dominance both in gut and lung. It has been shown that the high fiber diet can decrease the incidence of asthma.[6] Most studies of the PM focused on the bacterial population. However, it is expected that a variety of viruses and fungi are part of PM. All these microorganisms continuously communicate with each other and their host through their metabolites. Symbiosis is a dynamic, healthy state when PM has a ''normal'' diversity, and the host response/immune tone is well-tuned and adjusted. As a result of immigration and poor elimination of a hostile pathogen, altered immune tone, i.e., acute stress suppresses immunity, the PM diversity is reduced, and a

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dominant microorganism can act as a virulent pathogen, that provokes an inflammatory host response which is called the clinical phenotype of pneumonia. Bos et al. summarized this process as ''pneumonia could be defined in ecological terms as ''the acute loss of biodiversity due to the overgrowth of a single or several pathogenic microorganisms causing lung inflammation and damage.''[4]

It seems that PM diversity in a healthy state correlates with mouth microbiome diversity. It is well documented that the change in the oral microbiome is related to the severity of acute illness rather than the admission unit of the patient. This finding emphasizes the detrimental role of the patient's altered immune response to severe stress and its role in transforming symbiosis to dysbiosis.[7]

The practical question is how this new concept of developing pneumonia will change our diagnostic, therapeutic, and health administration policies of pneumonia. First, one cannot draw a sharp line between rigid definitions of ''community-acquired pneumonia'' vs. ''healthcare-associated pneumonia'' or ''ventilator-associated pneumonia.''

Increasingly, we encounter patients without a history of exposure to a health care environment that presents with Pseudomonas or Acinetobacter pneumonia. Based on the new concept, one can imagine that even a healthy person would have a few pathogenic gram-negative rods or gram-positive cocci in lower airways or alveolar epithelium. If PM diversity and immune tone maintain symbiosis, those pathogens will be contained and do not evoke a pathologic inflammatory response. In this view, even acute mental stress by changing the submucosal immune tone can promote dysbiosis and finally manifest as gram-negative rod (GRD) pneumonia.

This would account for the fact that, if a patient is being treated as ''community-acquired pneumonia'' with Ceftriaxone and Azithromycin, while the pathogen is an enteric GRD or methicillin-resistant staphylococcus aureus (MRSA), there would be a higher risk of treatment failure, morbidity, and mortality. To apply the personalized or precision medicine principles to patients with pneumonia, there are no other options than to optimize respiratory sampling and employ non-culture based microbiologic harvesting methods to detect the pathogenic microorganism(s) and tailor antibiotics against them. There is no doubt that shortly our guidelines will be changed to embrace the new concept and methodologies. Still, until then, for practitioners, the take-home message is by considering the new definition of pneumonia based on PM dynamics, we should be able to detect treatment failures faster and tailor antibiotics accordingly.

Applying the new concept to reimbursement policies by third-party payers as well as epidemiological studies, will uproot the current practices. For example, in the US, Medicare needs to revise its penalties based on narrow definitions of ventilator-associated pneumonia.

In conclusion: advancements in non-culture-based microorganisms detecting methods show that the lung has its dynamic microbiome that interacts with the host through symbiosis and causes pneumonia through dysbiosis. This concept will open the door for personalized/precision medicine in the diagnosis and treatment of pneumonia.

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