

# The aging lung

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**Abstract:** There are many age-associated changes in the respiratory and pulmonary immune system. These changes include decreases in the volume of the thoracic cavity, reduced lung volumes, and alterations in the muscles that aid respiration. Muscle function on a cellular level in the aging population is less efficient. The elderly population has less pulmonary reserve, and cough strength is decreased in the elderly population due to anatomic changes and muscle atrophy. Clearance of particles from the lung through the mucociliary elevator is decreased and associated with ciliary dysfunction. Many complex changes in immunity with aging contribute to increased susceptibility to infections including a less robust immune response from both the innate and adaptive immune systems. Considering all of these age-related changes to the lungs, pulmonary disease has significant consequences for the aging population. Chronic lower respiratory tract disease is the third leading cause of death in people aged 65 years and older. With a large and growing aging population, it is critical to understand how the body changes with age and how this impacts the entire respiratory system. Understanding the aging process in the lung is necessary in order to provide optimal care to our aging population. This review focuses on the nonpathologic aging process in the lung, including structural changes, changes in muscle function, and pulmonary immunologic function, with special consideration of obstructive lung disease in the elderly.

**Keywords:** aging, lung, pulmonary immunology, COPD

## Introduction

Pulmonary disease has significant consequences for the aging population. Chronic lower respiratory tract disease, defined as asthma, emphysema, chronic bronchitis, bronchiectasis, and chronic obstructive pulmonary disease (COPD), is the third leading cause of death in people aged 65 years and older.<sup>1</sup> According to 2010 census data, 13% of the US population, or 40.3 million people, are older than age 65, which is higher than any previous census. Additionally, the population is aging at an increasingly faster rate each year. Between 2000 and 2010, the population age 65 years and over increased by 15.1% compared to the total US population which only increased by 9.7%.<sup>2</sup> With such a large and rapidly growing aging population it is critical to understand how the body changes with age and how this impacts the entire respiratory system. Understanding the aging process in the lungs is necessary in order to provide optimal care to our aging population.

## Structural and functional changes with age

The structure of the thoracic cavity, which houses and protects the lungs, is vital for optimal lung function. Changes to the spine, muscles, and ribs over time with aging

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impact normal lung function. As people normally age, narrowing of the intervertebral disk spaces causes kyphosis or curvature of the spine.<sup>3</sup> This curvature decreases the space between the ribs and creates a smaller chest cavity.<sup>4</sup> While a small amount of anterior curvature or kyphosis of the thoracic spine is normal, an angle greater than 40°, which is the 95th percentile of normal, is defined as hyperkyphosis.<sup>5,6</sup> After age 40, the kyphosis angle begins to increase more rapidly in women than men, from a mean of 43° in women aged 55–60 years, to a mean of 52° in women 76–80 years of age.<sup>5</sup> The prevalence and incidence of hyperkyphosis is reported in older adults varying from approximately 20%–40% among both men and women.<sup>5,6</sup> In a study of 55 nonsmoking women with variable degrees of thoracic kyphosis Lombardi et al<sup>7</sup> found that with increasing vertebral angle there was a significant decline in the fraction of exhaled volume in 1 second (FEV<sub>1</sub>) and vital capacity (VC) during spirometry testing.<sup>7</sup> This effect was most significant once the kyphotic angle was over 55°. Culham et al hypothesized that this effect is not from a decrease in thoracic cavity size alone, but due to the rib space narrowing, which decreases the length of the intercostal muscles.<sup>8</sup> The angle of the muscle fibers in relation to the ribs may also affect the efficiency and decrease the movement of the lower ribs during inspiration.<sup>8</sup> These changes are structural and based on the origin and insertion of the muscles.

In addition to structural changes, there are changes in intrinsic function of the muscles with age. Overall muscle function in the body decreases by 2% annually as we age.<sup>9,10</sup> Aging is associated with reduced inspiratory and expiratory respiratory muscle strength.<sup>11</sup> Respiratory muscle decline can lead to an inability to ventilate in the face of increasing demands, such as that seen in respiratory disease. There is also evidence that at the cellular level, the muscles of elderly individuals have less mitochondrial adenosine triphosphate reserves to sustain a sudden increase in metabolic demand.<sup>12</sup> If an elderly person becomes ill with pneumonia, and therefore has increased metabolic demands for oxygen in the setting of decreased respiratory muscle strength, decreased cellular energy reserve, and decreased overall muscle function, he or she may not be able to meet those demands. This leads to an increased risk of respiratory failure in older individuals.<sup>13</sup>

With aging there is a decreased ability to clear mucus from the lungs. Two mechanisms primarily contribute to this decline: 1) reduced cough strength and 2) alterations in the body's ability to clear particles in the airways. First, cough plays a vital role in clearing mucus from the airways.

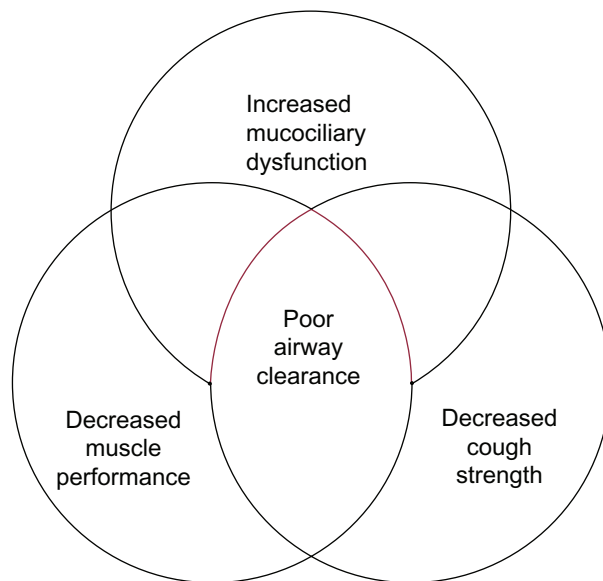
Coughing is a maneuver that requires generation of a high forced expiratory flow. During a cough maneuver, inspiratory muscles contract to allow the lungs to take in a large tidal volume necessary to augment a sustained high expiratory flow.<sup>14</sup> Next, the expiratory muscles contract to build high positive intrapleural and intraairway pressures for the development of peak expiratory flow rates.<sup>15</sup> Finally, when the glottis is opened, the cough occurs, and the mucus is expelled from the airway into the mouth. Any decrease in the strength of the respiratory muscles will greatly impact an individual's ability to generate the force required for an effective cough.<sup>16</sup> Aging is associated with both inspiratory and expiratory respiratory muscle strength reduction.<sup>11</sup> Polkey et al showed a 13% decrease in transdiaphragmatic pressure gradients, a surrogate for diaphragm strength, in older subjects (ages 67–81) as compared to younger subjects (ages 21–40).<sup>17</sup> Tolep et al compared the maximum transdiaphragmatic pressure (Pdimax) obtained during voluntary maximal inspiratory efforts in nine young (19–28 years) and ten elderly (65–75 years) subjects and found that the average Pdimax of the elderly subjects (128 ± 9 cm H<sub>2</sub>O) was significantly lower than the average Pdimax of the younger subjects (171 ± 8 cm H<sub>2</sub>O).<sup>18</sup> More specifically, there is age-related atrophy of muscle fibers, termed sarcopenia, which may also explain the reduced respiratory strength in the elderly. The decrease in muscle fiber strength can be as high as 20% by age 70.<sup>18–21</sup> There are complex changes involving the mitochondria, muscle fiber disorganization, age-related muscle fiber transitions, and metabolic shifts in the aging muscle that can also explain the reduction in muscle strength.<sup>22</sup>

The mucociliary elevator refers to the action of ciliated cells along the upper and lower airway to beat in synchrony, trapping and clearing mucus and foreign particles out of the lungs.<sup>23</sup> The upper airway nasal mucociliary cells work to remove large particles before they enter the smaller airways, and the lower airway mucociliary cells remove fine particles from the airway over a longer period of time.<sup>24</sup> There are alterations in both the clearance of large and small particles with aging. De Oliveira-Maul et al used the clearance of saccharin that was inhaled through the nares of healthy subjects to measure large airway nasal mucociliary function. They demonstrated that in people over age 40, there was a delayed nasal mucociliary clearance time of saccharin compared to subjects under 40 years of age.<sup>25</sup> Using radiolabeled particles that can travel past the upper airway and enter into the smaller airways in healthy nonsmoking subjects, Svartengren et al evaluated clearance of the labeled particles in different age groups ranging from age 19–81 years. They found that age

alone was negatively associated with airway clearance of radiolabeled particles at 1, 2, 7, 14, and 21 days.<sup>26</sup> The association between age and decreased clearance by the mucociliary elevator may be due to beat frequency of the cilia. The studies of beat frequency in cilia are confounded by the presence of cigarette smoking, which has a large impact on beat frequency. Age has not been a statistically significant predictor of decreased beat frequency.<sup>27</sup> The impact of structure and functional changes created by the aging process is summed up in Figure 1.

## Aging and inflamm-aging

In addition to these age-related structural changes in the lung, advanced age contributes to systemic immune dysfunction. Of particular interest is the basal activation of the innate immune system in aged individuals in the absence of an immunologic threat.<sup>28</sup> This phenomenon, referred to as “inflamm-aging”, is marked by elevated levels of tissue and circulating proinflammatory cytokines in aged subjects.<sup>28</sup> Specifically, increased levels of interleukin (IL)-1 $\beta$ , IL-6, and tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ) have been observed in aging rodent and human studies.<sup>29–32</sup> Theoretically, heightened levels of these cytokines in the absence of an immunologic threat or infectious target may be a contributory factor to reduced elasticity and destruction of the delicate lung parenchyma with advanced age. Related to inflamm-aging is the blunted immune response, known as “immunosenescence”, following a pathogenic threat or tissue injury.<sup>28</sup> Multiple studies have established reduced levels of mediators such as TNF- $\alpha$ ,



**Figure 1** The physiologic changes in aging which place elderly patients at risk for poor airway clearance.

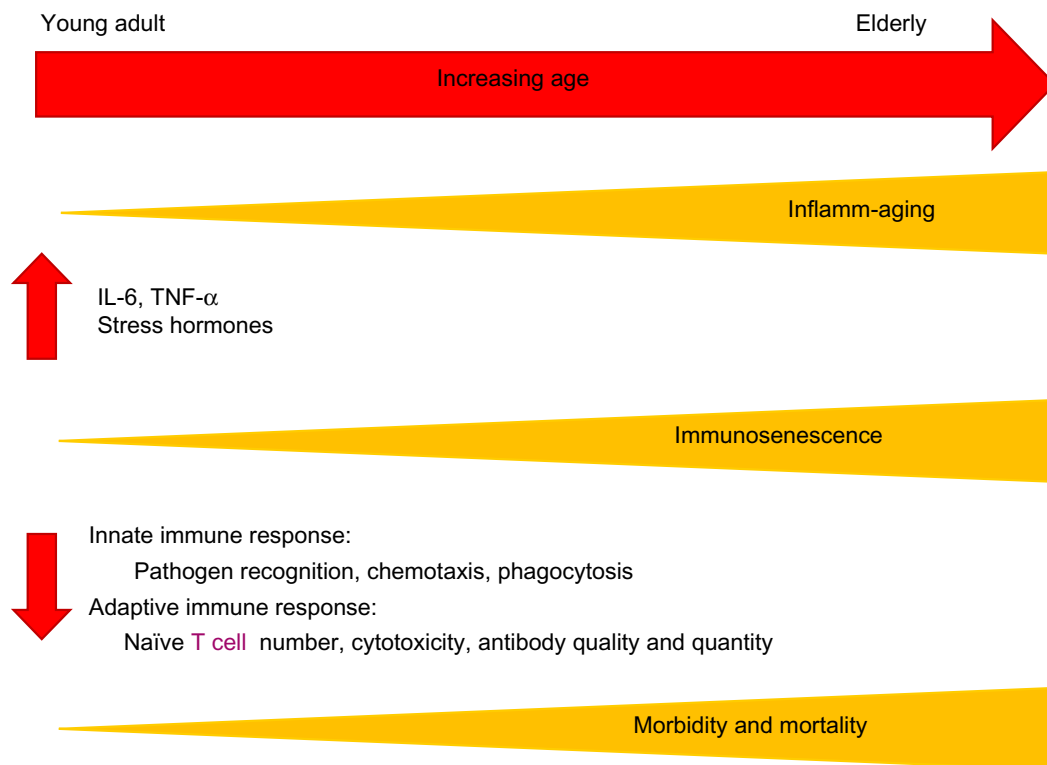
IL-6, interferon- $\gamma$ , nitric oxide, monocyte chemoattractant protein-1, and macrophage inflammatory protein-1 $\alpha$  after different types of antigenic stimulation in aged animals.<sup>33–38</sup> This basal level of inflammation, for example, elevated levels of IL-6, has been suggested to contribute to this subsequent immunosenescence following an immune challenge.<sup>28,39</sup> Using a model of IL-6 knockout mice, Gomez et al demonstrated restoration of cytokine production of IL-1 $\beta$ , IL-12, and TNF- $\alpha$  following lipopolysaccharide (LPS) challenge in aged IL-6 knockout animals to levels comparable to young wild-type.<sup>40</sup> These data suggest that the basal elevation of circulating IL-6 observed in aged wild-type animals prior to stimulation may contribute to the inability to upregulate cytokine production in the presence of an infectious threat as represented by LPS.<sup>40</sup> In addition to these cytokine alterations with aging, more recent data demonstrate a role for microRNAs in inflamm-aging and cellular senescence.<sup>41</sup> Specifically, microRNA 146a has been associated with a “senescent associated proinflammatory status” in the setting of vascular remodeling.<sup>42</sup> Together, these data support the relationship between inflamm-aging and immunosenescence, suggesting that a disruption in the balance of pro- and anti-inflammatory mediators results in a baseline proinflammatory environment with advanced age that subsequently dampens an appropriate innate and adaptive immune response (Figure 2).

In addition to this reduced activation, there are data that support a shift in the temporal response to injury with aging, such that this initial immunosenescence over time results in a protracted immune response and chronic inflammation.<sup>43,44</sup> These studies will be discussed in depth later in the context of pulmonary inflammation with aging; however, it is important to consider that this imbalance of immune mediators, delayed immune activation, and protracted course of inflammation may result in increased morbidity and mortality in aging individuals following infection, environmental exposures, or systemic injury.<sup>45–48</sup>

## Age and pulmonary immunity

The lung has immunologic defenses that are both complex and resourceful, utilizing both an innate and adaptive immune response to inhaled antigens. Innate immunity is the critical first line of defense for the lungs. Adaptive immunity (acquired immunity) is antigen-specific and is required to ward off encapsulated bacteria, viruses, and intracellular pathogens. This form of immunity relies on immunologic memory and lymphocyte production of antibodies to nonself threats. Some important changes in the innate immunologic response occur with aging. Toll like receptors (TLRs) are key

## The aging immune system



**Figure 2** Increasing age leads to elevated basal levels of inflammation (inflamm-aging) and increased immunosenescence, which are associated with changes in both innate and adaptive immune responses, contributing to the heightened morbidity and mortality seen in the elderly.

**Abbreviations:** IL, interleukin; TNF, tumor necrosis factor.

molecules in recognition and initiation of the innate immune response. In the context of aging, there are conflicting data regarding the impact of age on murine and human expression of TLRs or downstream signaling mediators.<sup>38,49–51</sup> While some of these murine studies on monocytes and macrophages report reduced expression of one or several TLRs,<sup>34,49</sup> another report demonstrates alterations in downstream TLR signaling involving p36.<sup>51</sup> Reduction in p38 signaling is supported by studies in human monocytes from aged subjects, where dampened p38 signaling was associated with diminished phosphorylation of p38.<sup>37</sup> Additionally, these authors observed a reduction in TLR1 but no changes in TLR2 expression. While the data are divergent on how aging impacts TLR expression, the data do suggest that alteration in the TLR pathways plays a role in an age-related aberrant initiation of the innate immune response and may contribute to an inability in rapidly recognizing and eradicating a pathogen. In studies of cigarette smoke exposure, elevated expression and nuclear translocation of nuclear factor- $\kappa$ B murine neutrophil chemokines, CXCL1 and CXCL2, were observed in aged mice.<sup>52</sup> This was accompanied by a protracted

neutrophilia in the lung parenchyma.<sup>52</sup> Moreover, following exposure to environmental toxins such as diesel exhaust, the increased pulmonary neutrophilia in lung parenchyma led to congestion and delayed clearance in aged animals as compared to young mice.<sup>53</sup> These data suggest that inhaled pollutants cause a prolonged, aberrant pulmonary immune response, which may translate into increased tissue damage, playing a part in environmental, age-related pathology like COPD. Pulmonary infection with *Francisella tularensis* in aged rodents demonstrated delayed production of neutrophil chemokines in conjunction with an attenuated neutrophil recruitment at early time points,<sup>43</sup> supporting the concept of an aberrant initial immune response with age. At later time points, inoculation of LPS into the respiratory tract of aged mice was associated with subsequent heightened levels of chemokines CXCL1 and CXCL2, IL-1 $\beta$ , and lingering pulmonary neutrophilia at 72 hours in aged animals as compared to young.<sup>44</sup> Considering the delicate lung alveolar architecture and the highly hydrolytic enzymatic degranulation products of activated neutrophils, this may contribute to excessive tissue damage and reduced lung function over time.

In addition to age-related perturbations in recruitment following inhalational injury or infectious insult, McLachlan et al examined cytotoxic activity of monocytes in older patients compared to younger patients in response to LPS exposure, and found that older patients display less reactive oxygen species (ROS).<sup>54</sup> Cytotoxicity generated by the production of ROS and reactive nitrogen intermediates (RNI) is a key function of M1, or proinflammatory macrophages, responsible for activating the Type 1 helper T cells (Th1) pathway. Alteration in macrophage polarization marked by reduced ROS and RNI is reported with advanced age.<sup>55</sup> Supporting the study by McLachlan et al, alveolar macrophages from aged rats had reduced basal and LPS-activated levels of ROS and RNI.<sup>56</sup> Our lab and others have also demonstrated that aging is associated with lower levels of inducible nitric oxide synthase (iNOS), an enzyme that regulates production of ROS and RNI under control of the interferon- $\gamma$  receptor.<sup>57,58</sup> In conjunction with these changes in macrophage phenotype and cytotoxicity, others found that neutrophils from older individuals ( $\geq 85$  years) produced less superoxide.<sup>54,59</sup> These changes in reactivity have implications for compromising host defenses with age.

In addition to changes in innate system functioning with age, there are changes seen in adaptive immunity with age. In order to activate B- and T cells, dendritic cells (DCs) must migrate from sites of tissue injury and infection to local lymph nodes. Several studies demonstrated DCs from aged mice show poor migration and homing. DC migration in response to chemokine ligand-21, a key DC chemokine that is localized in lymph nodes and binds chemokine receptor type 7 and presents on DC cell membranes, was reduced in aged mice as compared to young.<sup>60</sup> Interestingly, following respiratory infection in the lungs of aged mice with either mouse hepatitis virus-1, respiratory syncytial virus, influenza A virus, or severe acute respiratory syndrome coronavirus, elevated expression of prostaglandin D<sub>2</sub> correlated with reduced homing of lung DCs to regional lymph nodes and T cell activation.<sup>61</sup> Functional antagonism of prostaglandin D<sub>2</sub> resulted in upregulation of chemokine receptor type 7, the critical receptor for DC migration, and improved DC homing to draining lymph nodes, subsequently improving T cell activation and survival after viral infection.<sup>61</sup>

There are many adaptive immune functions that are inefficient with age. The thymus is primarily responsible for producing naïve T cells and is replaced by fatty tissue by age 60 years.<sup>62</sup> This leads to an increase in memory T cells relative to naïve T cells.<sup>63</sup> Both naïve CD4+ and CD8+ T cells are reduced in aged animals and humans relative to their memory

T cells counterparts.<sup>64-66</sup> In regard to CD8+ T cells, it has been suggested that repeated or latent cytomegalovirus infection may result in expansion of CD8+ memory cells, again diminishing the naïve CD8+ T cell pool.<sup>67</sup> Moreover, the proliferative aptitude of CD4+ T cells from aged donors appears to be reduced following T cell receptor engagement with high-dose anti-CD3 antibody in comparison to young controls,<sup>68</sup> suggesting a weaker novel pathogen-specific immune response. Meyer et al looked at the ratio of CD4+ to CD8+ T cells in bronchoalveolar lavage fluid in young versus old normal volunteers and found an increase in CD4+/CD8+ ratio as a function of age, suggesting there are fewer naïve cells available to be converted to memory cells in the face of a novel infection.<sup>69,70</sup> Recently, forkhead box N1, a transcription factor known to play a role in embryonic thymus development, has been shown to play a critical role in preventing thymic involution and preservation of naïve T cell subsets with aging.<sup>71</sup> Overexpression of forkhead box N1 was demonstrated to increase early thymic progenitors, decrease splenic CD4+ memory T cells, and increase splenic naïve CD4+ and CD8+ T cells.<sup>71</sup> These data suggest a possible potential target to increase the number of naïve T cells in aged individuals, increasing the ability of the elderly to respond to novel antigens. The antibody-secreting capacity of B cells is reduced with age, perhaps leading to a less robust immunologic response.<sup>72</sup>

## Aging and respiratory disease development

The prevalence of COPD is two to three times higher in people over age 60.<sup>73,74</sup> It is projected that from 1990 to 2020, COPD will move from the sixth to the third leading cause of death worldwide.<sup>75</sup> The Rotterdam study found that of healthy 55-year-olds without COPD, one in six women and one in four men will develop COPD later in life, with the risk for developing COPD over the coming 40 years being 24% and 16%, respectively.<sup>76</sup> Cigarette smoking is the greatest risk factor for developing COPD in genetically susceptible individuals. COPD is characterized by airway and lung inflammation, mucociliary dysfunction, alveolar destruction, and airway fibrosis.<sup>77</sup> The increased burden of COPD seen in the elderly population may be due to age-associated changes in the structure and function of the lung, increasing the pathogenetic susceptibility to COPD. These changes, described in elderly lifelong nonsmokers, are characterized by airspace dilatation resulting from loss of supporting tissue without alveolar wall destruction, similar to changes seen with COPD.<sup>77</sup> The Global initiative for chronic Obstructive Lung Disease (GOLD) criteria, accepted by the American Thoracic Society and the



European Respiratory Society, is the standard for the diagnosis and classification of COPD, and is assessed by measuring the ratio of FEV<sub>1</sub> to the forced vital capacity (FVC).<sup>78</sup> FEV<sub>1</sub> peaks between ages 20–36 years, and then begins to decline as we age.<sup>79</sup> The annual rate of decline after the age of 25 is 20 mL per year and further declines to a loss of 38 mL per year after age 65.<sup>79</sup> FVC begins to decline later in life than FEV<sub>1</sub> and at a slower pace. Because of the unparalleled rate of decline, use of the FEV<sub>1</sub>/FVC ratio alone to diagnose COPD will over represent a COPD diagnosis when no such pathology may exist.<sup>80</sup> To complicate this matter, Ohar et al found that COPD is underdiagnosed in the United States, arguing that this is due to underutilization of spirometry as a screening test for COPD.<sup>81</sup> Therefore, it is recommended to practitioners that a combination of spirometry and symptoms typical of COPD be utilized in the diagnosis of COPD in the elderly.

COPD is often associated with multiple comorbidities which can effect overall severity of disease. These include osteoporosis, mental illness, malnutrition, risk of cardiovascular disease, and skeletal muscle dysfunction.<sup>82</sup> Low body mass index is commonly seen in patients with COPD and has been shown to be inversely related to mortality in COPD.<sup>83,84</sup> Anxiety and depression are prevalent comorbidities and have also been shown to be related to negative outcomes in COPD. It is estimated that 40% of individuals with COPD have depression, compared to a prevalence of 15% in the general population.<sup>85</sup> Cognitive impairments are common and associated with COPD in the elderly. It is estimated that anywhere between 42%–70% of aged persons with COPD have concomitant dementia or neurocognitive impairment.<sup>86–88</sup> This may be related to hypoxemia and hypercapnia associated with COPD.<sup>89</sup> It may also be due to the common occurrence of cardiovascular disease in elderly with COPD.<sup>90</sup> These conditions certainly impact the ability to tolerate and comply with prescribed COPD therapies.

Inhaled bronchodilator therapy is the mainstay of treatment for the management of COPD. Treatment options are varied and include metered dose inhaler, dry powder inhaler, or nebulized formulations. There are many factors which may impact effective treatment use in the elderly COPD population including arthritis, weakness, poor manual dexterity, cognitive impairments, and visual limitations.<sup>91</sup> Careful consideration regarding treatment recommendations must be made in the aging COPD population.

## Summary

There are many age-associated changes in the respiratory and pulmonary system. The size of the thoracic cavity

decreases, limiting lung volumes and altering the muscles that aid in respiration. Muscle function on a cellular level is less efficient and has decreased reserve. Cough strength is reduced in the elderly population due to anatomic changes and muscle atrophy. Clearance of particles from the lung through the mucociliary elevator is negatively impacted and associated with ciliary dysfunction. There are many complex changes in immunity with aging that increase susceptibility to infections, including a less robust immune response from both the innate and adaptive immune systems. Finally, COPD has the highest prevalence in the elderly and deserves special consideration in regard to treatment in this fragile population. Additional research is needed to improve our understanding of the determinants of lung aging and the effects on lung immunity.

## Disclosure

The authors report no conflicts of interest in this work.

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