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Consequences of Pneumonia in Older Adults

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Synonyms

Catastrophic disability; Immunosenescence; Pneumonia; Post-influenza pneumonia; Post-pneumonia cognitive decline; Post-pneumonia myocardial infarction; Post-pneumonia sequelae

Overview

In most industrialized countries, pneumonia (often classified as influenza and/or pneumonia) is the only infectious disease in the top 10 causes of death (Statistics Canada 2018). In contrast to the developing world where pneumonia frequently kills children, in industrialized nations most of these deaths are in older adults (55+ years). Pneumonia is an insidious infection as it accelerates the development of seemingly unrelated chronic health conditions and can precipitate a decline in health and independence. Older adults who are hospitalized for community-acquired pneumonia have an increased risk of mortality (unrelated to pneumonia) in the next 5 years and increased risk of subsequent hospitalization (Yende et al. 2007). One study of American Medicare recipients reports that those who acquire pneumonia during a hospital stay have 2-year mortality rates that are twice as high as those who do not acquire pneumonia and they accrue an extra $15,000/year in health-care costs, primarily due to the development other chronic inflammatory conditions (Thomas et al. 2012). Having pneumonia in mid- to late-life is associated with increased risk of developing cardiovascular disease (Singanayagam et al. 2012; Corrales-Medina et al. 2015a), depression (Davydow et al. 2013, 2014), metabolic disorders (Yende et al. 2007), and dementia (Shah et al. 2013; Tate et al. 2014). Older adults who are hospitalized for pneumonia, even those who had no functional impairments, are likely to become impaired in the activities of daily living (Davydow et al. 2013). These post-pneumonia sequelae are the reason that the Ontario Burden of Infectious Disease Study lists pneumonia as the most economically costly infectious disease due to years of life lost and reduction in health-adjusted life years (Kwong et al. 2010).

Disturbingly for those of us who are getting older, or care for an older adult, is that this

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increase in mortality and declining health is independent of comorbid conditions. This means that having pneumonia in mid- to late-life reduces the years of good health in otherwise healthy, active older adults. Although pneumonia can be devastating to older adults in perfect health, it is even more problematic for those with pre-existing conditions. Individuals with chronic conditions such as cardiovascular disease, lung disease, diabetes, frailty, or cognitive decline are at increased risk of acquiring pneumonia and have poorer outcomes after hospitalization (Shea et al. 2014). There is a strong case to be made that age is less of a risk factor than the presence of multiple chronic conditions and frailty (Hak et al. 2004; Shea et al. 2014). Since socioeconomics and health are inextricably linked, individuals of lower socioeconomic status are more likely to have risk factors such as multiple chronic conditions and therefore are more likely to be hospitalized for influenza/pneumonia (Crighton et al. 2007; Grantz et al. 2016).

Key Research Findings

Severe Pneumonia Can Result in Widespread Organ Damage

Studies on the consequences of pneumonia have generally focused on events that occur in the airway. Yet, considerable clinical and laboratory evidence indicates that during severe pneumonia that results in bacteremia (~20% of hospitalizations), the responsible bacteria can gain access to and cause long-lasting damage in other vital organs. One of the most striking examples is the heart, where opportunistic pathogens such as *Streptococcus pneumoniae*, the leading bacterial cause of community-acquired pneumonia, kill cardiomyocytes, impair heart function, and prime permanent cardiac scarring in damaged heart tissue that presumably impairs contractility in survivors (Brown et al. 2014; Alhamdi et al. 2015; Gilley et al. 2016). Notably, the incidence of adverse cardiac events coincides with severity of infection, with individuals requiring admission into an intensive care unit having the highest rates of heart failure. As it is older adults who are most susceptible to severe pneumonia, it is also older individuals who are most susceptible to concomitant adverse cardiac events. Overall, ~20% of adults hospitalized for pneumococcal pneumonia experience an adverse cardiac event during hospitalization, and these individuals are fourfold more likely to die than those with pneumonia alone (Musher et al. 2007). Importantly, hospitalization for pneumonia and severity of pneumonia are also linked to greater incidence of adverse cardiac events and mortality in convalescence. This extends for a period of up to 10 years post-infection (Corrales-Medina et al. 2011, 2012, 2015a, b). Thus, the negative consequences of severe pneumococcal pneumonia on the heart are considerable and both acute and long-lasting.

Two other critical organ systems that can become damaged as result of severe pneumonia that results in invasive disease include the central nervous system and kidneys. *S. pneumoniae* and *Haemophilus influenzae*, also a common cause of bacterial pneumonia, are neurotropic and capable of crossing the blood-brain barrier to cause bacterial meningitis. In addition to having a 17–30% mortality rate, survivors of these types of bacterial meningitis typically have lifelong cognitive impairments (Erdem et al. 2014). Acute kidney injury also occurs during severe *S. pneumoniae* infection and is similarly linked to elevated mortality rates (Murugan et al. 2010; Lin et al. 2016). Thus, the notion that bacteria are restricted to the airway during pneumonia is not necessarily accurate. Moreover, the presence of bacteria in the bloodstream allows for disseminated organ damage, and this in turn has a harmful effect on not only hospital outcomes but also long-term survival and quality of life, as many of these individuals must now deal with the sequelae of these serious infections. Fortunately, effective vaccines against the most virulent version of *S. pneumoniae* and *H. influenzae* protect against invasive disease. Moreover, the influenza vaccine confers indirect protection against severe pneumonia by preventing co- or secondary infections. Thus, these disease states can potentially be avoided.

Cognitive Decline/Dementia

Life-threatening infections such as sepsis or inflammatory events (e.g., acute respiratory distress syndrome) are associated with cognitive decline that is evident even years after the event (Hopkins et al. 1999; Mikkelsen et al. 2009, 2012; Ehlenbach et al. 2010; Iwashyna et al. 2010). It has also been demonstrated that individuals with some degree of cognitive impairment or dementia have an accelerated decline in cognitive capacity after surgery, injury, or infections (Abildstrom et al. 2000; Holmes et al. 2003; Shah et al. 2013). What is surprising is that having pneumonia is strongly associated with cognitive decline even in cognitively intact individuals. This was explored in a well-controlled study by Tate et al. In this study, older adults took various cognitive tests every 6 months and were followed for at least 6 years. Approximately 7% of the participants ($n = 221$) developed pneumonia severe enough to be hospitalized but not severe enough to require an ICU stay (i.e., was not perceived as life-threatening). Those who had pneumonia were two times as likely to develop dementia over the 3 years of follow-up (HR = 2.3, CI: 1.6–3.2) than those who did not. Disturbingly, only individuals who showed no evidence of any cognitive impairment were included in this study, demonstrating that post-pneumonia cognitive decline occurs in otherwise healthy, cognitively intact individuals (Tate et al. 2014). Consistent with other studies (El Solh et al. 2006; Davydow et al. 2013), hospitalization for pneumonia is much more strongly associated with cognitive decline than hospitalization for any other reason (Tate et al. 2014). The general consensus is that between 20% and 38% of older adults hospitalized for pneumonia will develop dementia or become cognitively impaired earlier than expected (Torres et al. 2004; Tate et al. 2014; Girard et al. 2018), but since many of these studies have a relatively short follow-up period (<6 years), this may be an underestimate.

The mechanisms by which pneumonia precipitates cognitive decline or dementia are currently speculative. Elevated levels of serum cytokines and changes in behavior and cognition have been evident for decades. Older adults hospitalized for pneumonia have more pronounced and protracted inflammatory responses than younger adults (Bruunsgaard et al. 1999), and these increase in inflammation and delay in returning to homeostasis may contribute to poor outcomes including cognition (Yende et al. 2008, 2011). Indirect evidence for the role of soluble mediators in inflammation in post-pneumonia cognitive decline comes from observations that the risk of functional decline post-pneumonia is proportionate to severity of the infection (Torres et al. 2004). Further support for the risk of elevated cytokines contributing to cognitive was found in patients with Alzheimer's disease. Those with the greatest decrease in cognitive scores post-infection had the highest levels of serum IL1β (Holmes et al. 2003). Mechanistic evidence is lacking, but some studies have suggested that during neurodegeneration, microglia are primed to induce inflammatory responses and a secondary insult such as infection causes them to produce high levels of inflammatory cytokines, which perpetuate the state of inflammation (Cunningham et al. 2009). Along such lines, studies with animals have shown that exposure to bacterial cell wall products, which are highly inflammatory, alone results in the death of neurons in the dentate gyrus of the hippocampus (Orihuela et al. 2006).

Severe Pneumonia Can Unmask Underlying Metabolic Dysregulation

It is unclear whether having pneumonia in mid- to late-life increases the risk of developing diabetes or whether having pneumonia unmasks pre-existing conditions since metabolic dysregulation is a well-known risk factor for pneumonia (Kornum et al. 2008, 2010; Foltran et al. 2013). The observation that diabetics are more susceptible to pneumonia was made over a decade ago, and recent evidence indicates that this is due to hyperglycemia rather than comorbid conditions such as obesity (Kornum et al. 2007; Hirata et al. 2013; Alexopoulos et al. 2016). In fact, even in nondiabetics, careful management of hyperglycemia during hospitalization reduces mortality from life-threatening infections (van den Berghe et al. 2001, 2003). The mechanism by which blood glucose affects antibacterial immunity is unclear, although decreases in phagocytosis and cellular

recruitment to the site of infection have been reported (MacRury et al. 1989; Martinez et al. 2016a, b). Older adults are at higher risk of developing metabolic disorders and often have higher blood glucose levels, even in the absence of diabetes (Dharmarajan et al. 2016) which contributes to both susceptibility to pneumonia and outcome. Blood glucose levels at admission to hospital are a predictor of mortality, even in nondiabetic patients, and the elevation in blood glucose need not be extreme to increase mortality risk (Bagshaw et al. 2009; Lepper et al. 2012; Salonen et al. 2013; Akirov and Shimon 2016; Koskela et al. 2014; Schuetz et al. 2014; Akirov and Shimon 2016). This increased risk of mortality extends to as long as 5 years after release from the hospital at which time very few deaths are from pneumonia (Koskela et al. 2014; Akirov and Shimon 2016). To determine whether pre-existing and subclinical dysregulation of glucose metabolism contributed to pneumonia outcome, hospitalized patients had their postprandial levels of glucose measured during their entire hospital stay. Those with the highest spikes of blood glucose after a meal (even if fasting glucose fell in the normal range) had increased mortality 12 months after admission (Koskela et al. 2014). These data suggest that pneumonia uncovers rather than causes metabolic dysregulation in older adults.

Dysregulated Inflammatory Responses May Contribute to Post-Pneumonia Health Impairments

The inflammatory response is essential for surviving severe acute infections; however, excessive or prolonged inflammation causes pulmonary epithelial hyperpermeability and immunopathology and, in the case of pneumonia and influenza, is often the actual cause of death (Matthay et al. 2012). Levels of inflammatory markers are substantially higher in older adults and in frail inpatients (Palmer et al. 2019), and furthermore they are correlated with prognosis and adverse outcomes of pneumonia. For example, C-reactive protein (CRP) is elevated during acute infection and pneumonia and predicts adverse outcomes (Verschoor et al. 2014; Ticinesi et al. 2017). Similarly elevated interleukin (IL)-6 levels at either baseline or 1 week post-admission are predictive of 28-day mortality (Takahashi et al. 2016). It is likely that the ability to resolve inflammation following critical illness is a major determinant of prognosis. Studies have shown that patients with persistently high levels of CRP 3 months following discharge exhibit the poorest mobility (Griffith et al. 2016), and high CRP levels prior to discharge are a significant predictor of readmission (Gulcher et al. 2016). Available evidence suggests that older adults have excessive and prolonged inflammatory responses which contribute to mortality and post-influenza and pneumonia health impairments (Yende et al. 2008, 2011); however, mechanistic links between these inflammatory processes and outcomes of pneumonia and influenza have yet to be established.

Summary

Older adults have unacceptably high rates of hospitalization for pneumonia, ranging from >270/100,000 in 50–65-year-old to >4000/100,000 in those older than 85 (Storms et al. 2017). Of these hospitalizations between 20% and >30% are severe enough to require an ICU stay (Storms et al. 2017). Although having a pre-existing healthy condition or frailty increases the risk of hospitalization for pneumonia, even healthy older adults are likely to experience life-changing changes in health and independence as a result of infection. In fact, 5-year mortality rates for those hospitalized for pneumonia are as grim as those hospitalized for congestive heart failure, stroke, or major fracture (Yende et al. 2007).

The majority of pneumonia in older adults is caused by *Streptococcus pneumoniae* or results from post-influenza pneumonia, and consequently vaccination should be aggressively pursued to prevent not only the primary infection but also the long-term health consequences. Vaccination is admittedly less effective in older adults than children and young adults (Rudnick et al. 2013; Leventer-Roberts et al. 2015), although there is good evidence that even when it does not prevent infection, it improves outcomes by reducing time

in the ICU and heart attacks and increases the chance that the patient will be able to live independently post-discharge (Arriola et al. 2017). Because contact with children is a major risk factor for infection, effective vaccination strategies should include vaccinating whole communities (Loeb et al. 2010).

Vaccination may be the only strategy we have to prevent hospitalization for pneumonia; however, it is clearly not sufficient. In the immediate term, preventative strategies such as vaccination for influenza and pneumococcal pneumonia should be aggressively pursued in order to minimize these health consequences. Older adults who have had pneumonia should be considered at risk for developing other, seemingly unrelated, health issues. In the longer term, further research is required to understand the mechanisms by which pneumonia accelerates or exacerbates age-related health issues. Dysregulated inflammatory responses and an inability to resolve inflammation are potential mechanisms by which pneumonia and declining health may be linked.

Cross-References

- Age-Related Cognitive Impairment
- Aging and Health Disparities
- Dementia
- Diabetes Mellitus
- Frailty in Clinical Care
- Heart Attack/Myocardial Infarction
- Human Immune System in Aging
- Influenza Vaccination in Older adults
- Pneumonia

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