University of Texas Southwestern Medical Center
Internal Medicine Grand Rounds
June 20, 2014

The Evolving Paradigm of Pneumonia

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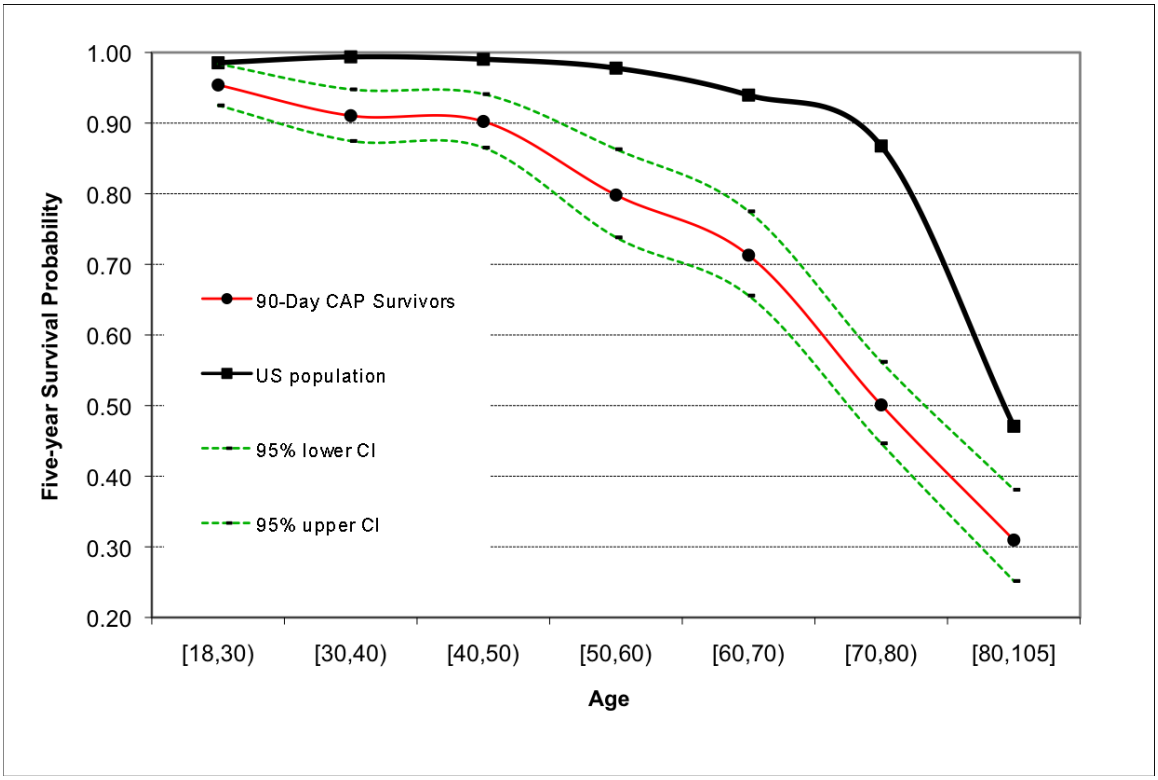


This is to acknowledge that Eric Mortensen, MD, MSc, FACP has disclosed that he does not have any financial interests or other relationships with commercial concerns related directly or indirectly to this program. Dr. Mortensen will be discussing potential off-label uses of statins and ACE inhibitors in his presentation.

Biographical Information:
Eric Mortensen MD, MSc, FACP received his medical degree from the Medical College of Pennsylvania, and completed his Internal Medicine residency training as well as a Fellowship in Outcomes Research at the University of Pittsburgh Medical Center. He also completed a Masters in Clinical Research at the University of Pittsburgh. He joined the VA North Texas Health Care System and UT Southwestern in 2011. His research has focused on the epidemiology of pneumonia and other common infections. Dr. Mortensen has authored/co-authored over 80 peer-reviewed articles, and his research has been supported by the National Institutes of Health, Department of Veterans Affairs, and Agency for Health Care Research and Quality. He is the director for the VA Cooperative Study Program clinical trial center at the Dallas VA Medical Center.

Purpose and Overview:
The goal of this presentation is review the research that examines the causes of death and disability for patients hospitalized with pneumonia as well as the impact of the episode of pneumonia on outcomes long after the initial infection has resolved.

Educational objectives:
1. Review the impact of pneumonia on long-term mortality and morbidity.
2. Review the relationship of infections on cardiovascular events.
3. Examine the incidence of pulmonary malignancy after pneumonia.

"Pneumonia may well be called the friend of the aged. Taken off by it in an acute, short, not often painful illness, the old man escapes those `cold gradations of decay' so distressing to himself and to his friends."

-Sir William Osler, Principles and Practices of Medicine [1]

Introduction

Pneumonia, along with influenza, is currently the eighth leading overall cause of death in the United States, and is the leading cause of infectious death [2]. However, this only considers the immediate impact of pneumonia on mortality. Almost all prior research on pneumonia has focused on outcomes in the first one to three months after presentation [3]. However there is growing interest in the effects of pneumonia after this immediate period. Despite Osler's statement, it is no longer clear that that the effects of pneumonia are limited to "…acute, short…." Although this may have been the case prior to the advent of antimicrobial therapy in the 1940's, recent studies have demonstrated that this assertion is probably not true. Despite the reduction in short-term mortality in the antibiotic era, there are still substantial long-term effects.

Review of the literature reveals that there are now several articles that explicitly examine long-term mortality after pneumonia and predictors of that mortality [4]. In these studies long-term mortality ranged from 13% at three years to 53% at 7 years, depending largely on the cohort source (e.g., outpatients, inpatients, the critically ill.) The few studies that were able to compare long-term mortality for those with pneumonia to those without, demonstrated that long-term mortality is significantly higher for those with pneumonia. For example, a large case-control study of hospitalized Medicare patients demonstrated that those hospitalized with community-acquired pneumonia had significantly higher long-term mortality than those hospitalized for other conditions (40.9% vs. 24.9%) [5].

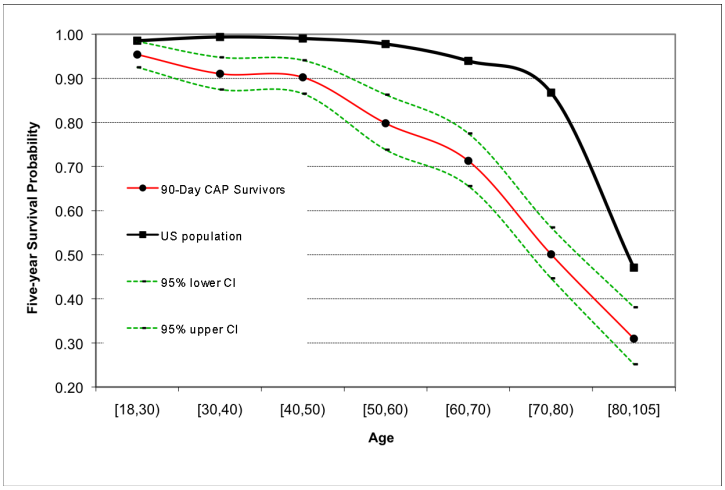
Studies of Long-Term Mortality

In 1998 Brancati et al. published the first study of long-term mortality after pneumonia [6]. They prospectively examined 141 patients hospitalized for pneumonia at 2 hospitals and examined mortality within 2 years after hospitalization. They found that 16% died during the initial hospitalization and that of those who survived the hospitalization (n=119) 32% died within the next

24 months. A history of moderate to severe comorbid conditions and hematocrit < 35% were associated with increased long-term mortality in the multivariable survival models. Interestingly they did not find an association between age and increased long-term mortality. However this study was limited by the small sample size and the fact that they did not exclude those patients who died during the hospitalization from their multivariable analysis, which may have biased their findings.

In a study performed as part of the Pneumonia Patient Outcomes Research Trial (PORT) cohort study, Mortensen et al. examined 1555 patients prospectively enrolled at 4 sites in the United States and followed them for a mean of 5.9 years [7]. They found that 8.7% died within the first 90-days after hospital admission and that of the remaining 1419 patients, 472 (30.3%) died before the end of follow-up. They found that as compared to the US population survival was significantly lower for almost all age groups who had pneumonia (Figure 1). After excluding those patients who died within 90-days, they found that factors such as age, do-not-resuscitate status, poor nutritional status, pleural effusion, glucocorticoid use, nursing home residence, high school graduation level or less, male sex, preexisting comorbid illnesses, and the lack of fever were associated with increased long-term mortality (Table 1). They compared survival in the pneumonia cohort to an age-matched cohort derived from life table data and demonstrated there was significantly lower survival for patients with pneumonia across all age groups. This study supported the results of Brancati that there was significant long-term mortality but demonstrated that there was no association with acute physiologic derangements.

Figure 1- Probability of surviving 5 years for those with pneumonia versus an age- and gender-matched US population



A study by Kaplan et al. examined 158,960 Medicare patients hospitalized with pneumonia who were age, race, and sex matched to 794,333 patients hospitalized for other conditions [5]. They demonstrated a 1-year mortality of 40.9% for the pneumonia group vs. 24.9% for the control group (P<0.001) (Figure 2.) When they restricted their analyses to only those who survived the initial hospitalization 1-year mortality for the pneumonia group was 33.6% vs. 24.9% for the control group (P<0.001.)

Table 1- Factors Independently Associated with Increased Long-Term Mortality among Patients who Survived 90 Days (n=1419)

Characteristic	Hazard Ratio	95% Confidence Interval
Age (per decade)	1.3	1.2-1.4
Charlson score		
0	1.0	
1-2	2.1	1.5-2.7
3-4	3.1	2.3-4.3
≥5	6.3	4.5-8.9
Do not resuscitate order at presentation	1.7	1.2-2.4
Poor nutritional status*	1.7	1.1-2.5
Less than a college education	1.6	1.2-2.1
Male gender	1.5	1.2-1.8
Pleural effusion on baseline chest x-ray	1.4	1.1-1.8
Feeling feverish	0.7	0.6-0.9
Corticosteroid use †	1.5	1.2-1.9
Nursing home residence	1.5	1.1-2.1

A study by Yende et al. examined 3075 subjects enrolled in a prospective observational study and studied long term mortality differences among patients hospitalized for various reasons, including cancer, fracture, congestive heart failure, cerebrovascular accident, and pneumonia over a 5 year period [8]. Of the 106 subjects hospitalized with pneumonia, 21% died within 1 year and 36% within 5 years, and subjects with pneumonia had higher long-term mortality than subjects hospitalized for other conditions (odds ratio 5.6, 95% confidence interval 2.8-11.2) (Figure 3). These studies illustrate the impact of pneumonia on long-term mortality compared to what many would consider even more important, medical conditions. Given the chronic, even progressive nature of many of these conditions, the results suggest that pneumonia may be associated with unmeasured underlying factors that negatively impact long term survival even more so than malignancy or heart failure, or alternatively, that pneumonia causes long term physiologic alterations that result in subsequent increased mortality.

Figure 2- Unadjusted and Adjusted Survival Curves for those with Pneumonia vs. the General Population (A) and Hospitalized Controls (A and B)

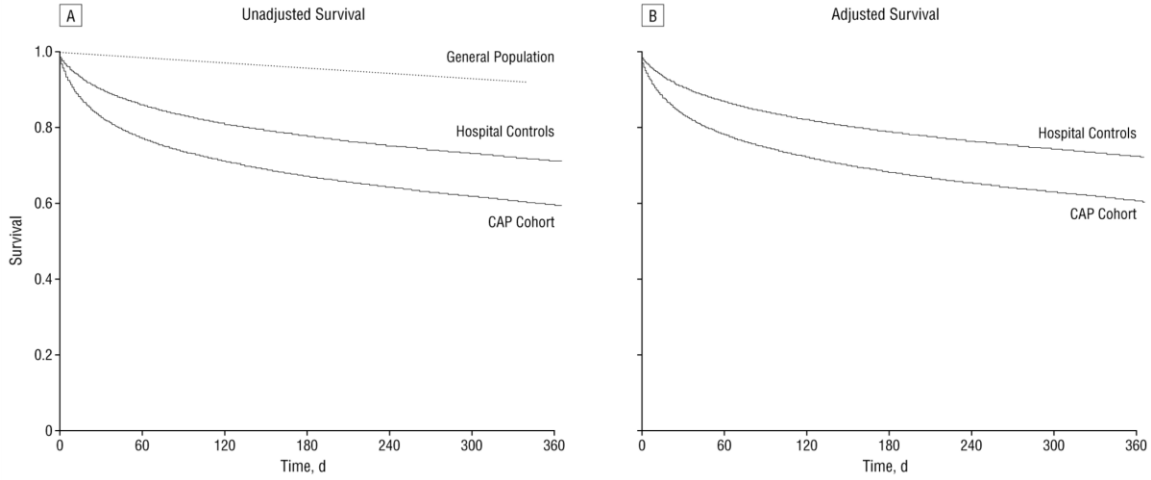
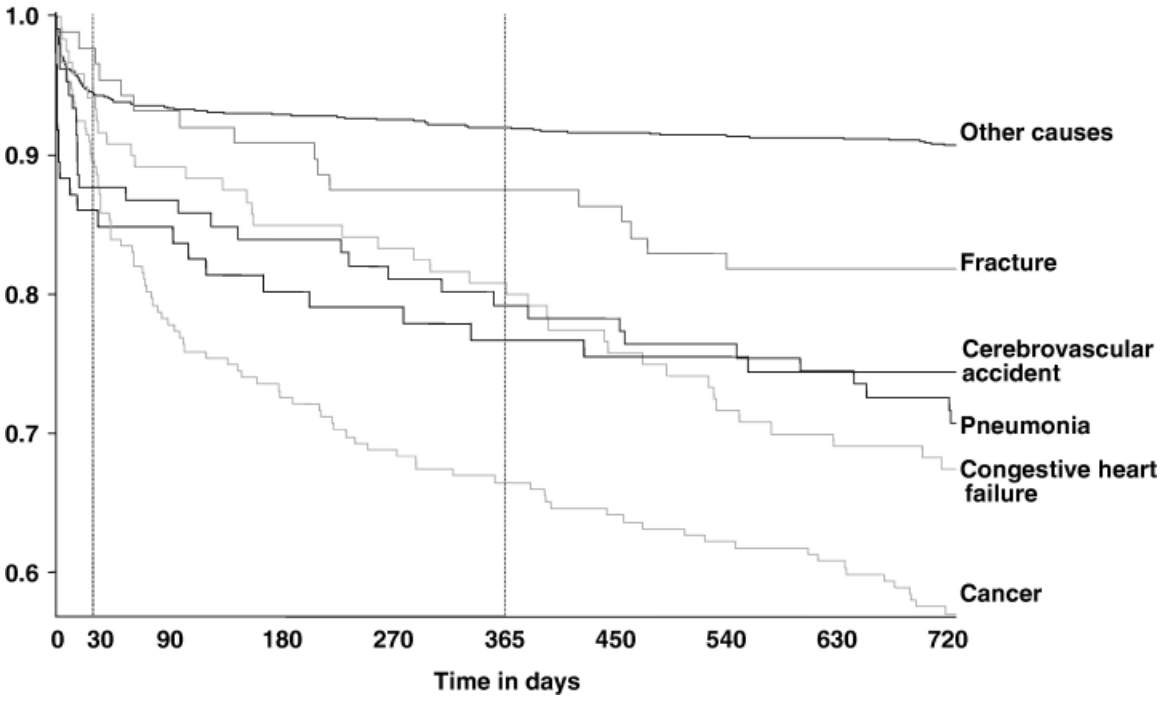


Figure 3- Long-Term Survival of Those Hospitalized with Pneumonia vs. Other Common Conditions



Guertler and colleagues [9] examined the prognostic performance of the pneumonia severity index [10] and other bio- and inflammatory markers on long-term outcomes after pneumonia. They examined subjects with community-acquired pneumonia who were enrolled as part of the ProHOSP trial, a multi-

center randomized controlled trial that tested whether a procalcitonin guided algorithm could reduce antibiotic exposure without increasing adverse outcomes. Subjects were followed up for 18 months after joining the study. Of the initial 925 subjects with pneumonia enrolled in the parent trial, 5.2% (n=48) died during the initial hospitalization and an additional 16.4% (n=152) died within 18 months. Similar to prior studies, they found in the multivariable models that male gender and pre-existing comorbid conditions such as chronic obstructive pulmonary disease and cancer were associated with increased long-term mortality. Interestingly, they also found that higher peak levels of pro-adrenomedullin (Pro-ADM) were associated with higher long-term mortality, and that history of chills, higher body temperature, and higher C-reactive protein (CRP) levels were associated with lower long-term mortality.

Sligl et al. examined the impact of premorbid functional status on 271 critically ill patients with pneumonia [11]. Mortality at 1 year in this cohort was 27%. They found that after adjusting for the pneumonia severity index [10], which includes many factors including comorbid conditions and demographic factors, that complete pre-hospital functional dependence was associated with increased 1-year mortality (hazard ratio 3.0, 95% confidence intervals 1.5-6.1).

Guertler and colleagues [9] found that higher peak levels of ProADM were associated with higher long-term mortality, and that history of chills, higher body temperature, and higher C-reactive protein (CRP) levels were associated with lower long-term mortality. These findings are somewhat counter intuitive as studies have demonstrated that a high inflammatory response is associated with worse short-term outcomes after pneumonia. However this study's findings, which were similar to those from the Pneumonia PORT cohort study [7], suggest that there are a number of patients with pneumonia who, although able to survive the initial episode of pneumonia, are not able to mount a normal immune response. This inability to mount a sufficient response may predispose these patients to subsequent mortality and morbidity due to other infectious diseases.

These studies demonstrate that even after survival of an episode of pneumonia, there are significant effects upon long-term mortality for up to several years after that episode. Predictors are primarily factors such as age, comorbid conditions, social factors (e.g., nursing home residence, educational status), and functional

status. Further research is needed to allow development of generalizable prediction models that will help physicians determine which of their patients are at higher risk for death in the years following an episode of pneumonia.

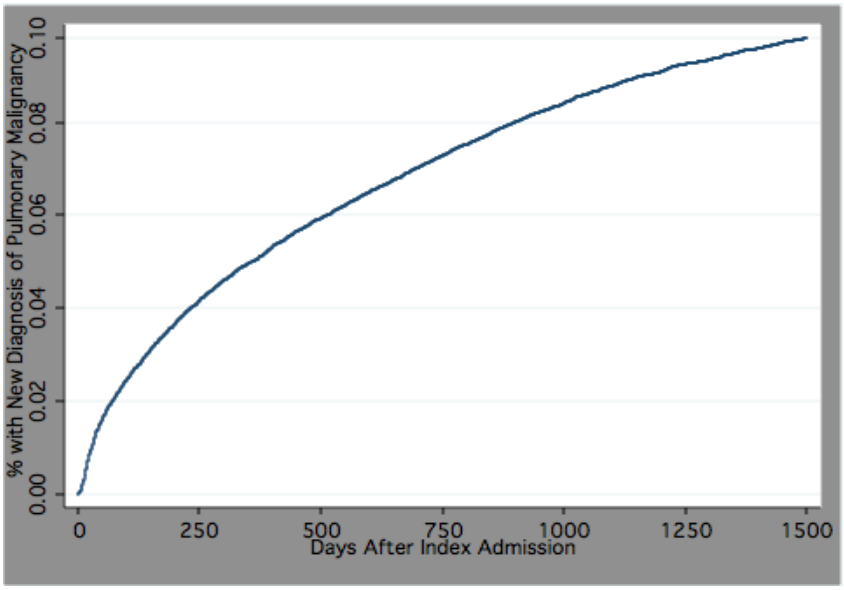
Although studies have clearly demonstrated that there is increased long-term mortality after pneumonia it is unclear what the potential reasons are and whether they are modifiable. Potential causes of this increased mortality include other comorbid conditions, cardiovascular events, malignancies, and chronically elevated pro-inflammatory cytokine levels.

Almost all studies that examined predictors of long-term mortality in patients with pneumonia have shown that an increasing number of comorbid conditions are associated with increased long-term mortality. Since pneumonia is much more common in those who are older or with multiple comorbidities this is unsurprising. Unfortunately most of the studies completed to date have examined comorbidities as composite scores, either as the Charlson comorbidity system [12] or pneumonia severity index, rather than as separate conditions. However, the studies that did separate comorbid conditions identified stroke, cardiovascular disease, chronic obstructive pulmonary disease, pre-existing malignancies, and HIV infection as risk factors for long-term mortality.

Pulmonary Malignancy

Although many physicians recommend that patients receive follow-up chest imaging after the diagnosis of pneumonia to ensure that a pulmonary malignancy is not missed, there is little research evidence to support this practice. A recent study suggests that up to 10% of veterans >65 years of age hospitalized with pneumonia are diagnosed with either a primary lung cancer or pulmonary metastasis (Figure 4) within several years of admission [13]. However it was unclear if the initial diagnosis of pneumonia was correct or was it that the patient actually had lung cancer at the time of initial admission, as clinical presentations can be quite similar. So it is quite possible that some of the observed long-term pneumonia-related mortality is due to pulmonary malignancies. Another recent study by Tang et al. demonstrated only 0.2% of patients having a new diagnosis of lung cancer within 5 years however this study of over 3000 patients hospitalized with pneumonia were at significantly lower risk of lung cancer with only 17% smokers and only 59% aged 50 years or older [14].

Figure 4- Incidence of Lung Cancer or Pulmonary Metastasis for Patients Hospitalized with Pneumonia

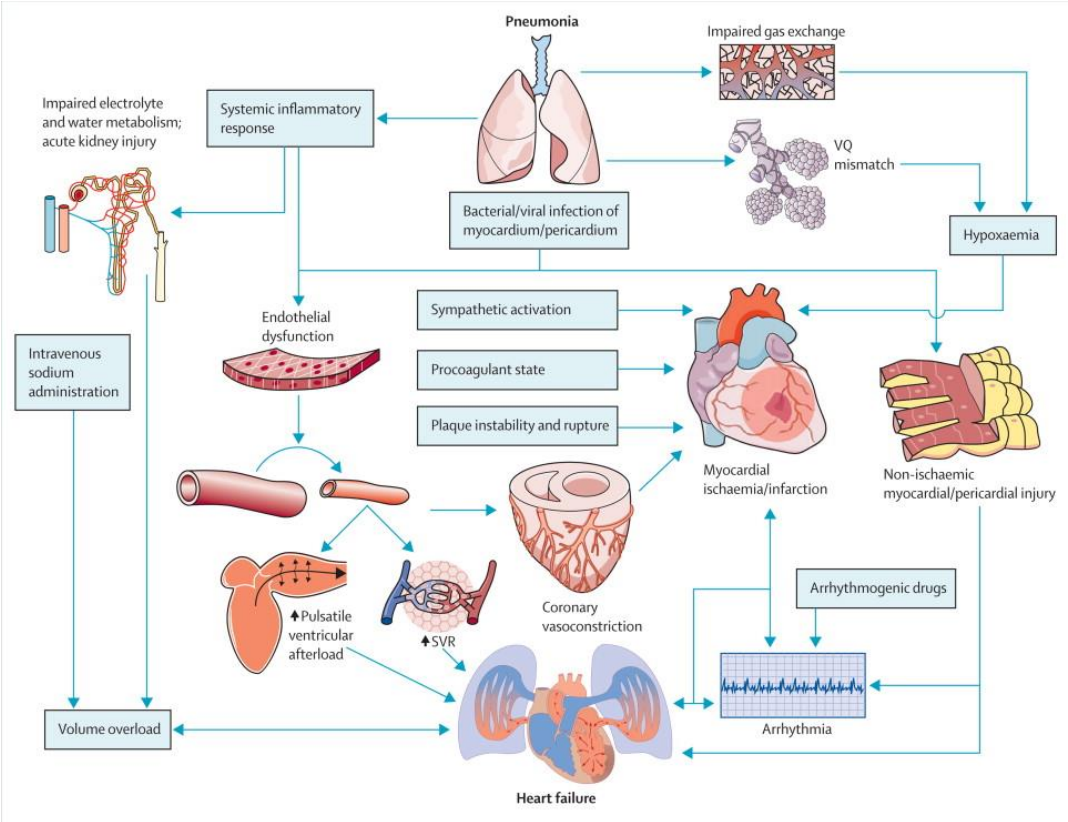


Cardiovascular Events

In addition, studies have suggested an increased risk of cardiovascular events during and after serious infections such as pneumonia, and it is suggested that cardiovascular events may play an important role in long-term outcomes [15]. Studies have suggested that many patients hospitalized with pneumonia continue to have elevated levels of pro-inflammatory cytokines even after recovering from the acute episode of pneumonia, which has been to be associated with increased risk of cardiovascular events. Influenza, Streptococcus pneumoniae, Staphylococcus aureus and Escherichia coli, which can all cause pneumonia and/or severe sepsis, have demonstrated the ability to either infect, or directly impair, cardiomyocytes, and cause conduction and contractility dysfunction. In addition, many comorbid conditions (e.g., diabetes, chronic kidney disease) and lifestyle factors (e.g., tobacco use, functional status) have been demonstrated to be associated with increased risk of both pneumonia/severe sepsis, mortality from these infections, and risk of CV events. Figure 5 demonstrates potential pathways between pneumonia and cardiovascular disease. Therefore it is quite possible that an important portion of this increased mortality is due to cardiovascular events. While earlier studies have classified such deaths occurring months after a pneumonia episode as non-pneumonia related, these data suggest that this may not be true. Furthermore,

studies have shown that for as long as 3-12 months after pneumonia and otherwise uncomplicated viral respiratory infections, the risk of vascular events including myocardial infarction, stroke, and venous thromboembolism remain increased relative to control populations. The increased rate of these events likely contributes significantly to the long-term mortality risk of pneumonia patients, whether or not the acute vascular event is fatal. Possible mechanisms for the increased risk of vascular events in patients with respiratory tract infections include endothelial dysfunction due to ongoing subclinical inflammation and/or ongoing presence of an inflammation induced pro-thrombotic state.

Figure 5- Potential Pathways by which Pneumonia May Cause Cardiovascular Events (Adapted from Corrales-Medicine 2010) [15]



A study by Perry et al. [Perry, 2011 #3134] examined the incidence of CV events including myocardial infarction (MI), heart failure (HF), unstable angina, cardiac arrhythmia, and stroke within 90 days of hospitalization for pneumonia. They used data from the administrative databases of the Department of Veterans Affairs and examined a cohort of subjects >65 years of age hospitalized with

pneumonia between October 2001 and September 2007.The entire cohort comprised 50,119 subjects with a mean age of 77.5 years (SD 6.7 years), and 98% of the cohort was male. The 90-day incidence of first-time CV events was 1.5% for MI, 10.2% for HF, 12.0% for arrhythmia, and 0.2% for stroke. The majority of events occurred during the reference hospitalization, especially first-time HF and arrhythmia.

CONCLUSION

It is clear that contrary to traditional beliefs that pneumonia is not only an "…acute, short, not often painful illness…" [1] but a condition that directly impacts patients' morbidity and mortality for a year or more after a single episode. It appears that both elevated and suppressed inflammatory responses after an episode of pneumonia may contribute to this increased mortality. Furthermore, patients with pneumonia have increased mortality rates compared to similar control populations for much greater than 1 year after the episode, but for these longer periods of time, the causal relationship is less clear. For example, pneumonia may be the initial presentation for other conditions that increase the risk of death, including lung cancer and subtle immune defects. Clinicians should monitor patients who survive an episode of pneumonia closely for malignancies, worsening respiratory function, cardiac conditions, and subsequent infections. Additional research is urgently needed to further examine the contributors to this long-term mortality and to identify methods to improve long-term survival for patients with pneumonia.

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