Introduction

Pneumonia remains a common cause of morbidity and mortality in the US. Although, community-acquired pneumonia (CAP) has traditionally been considered an acute process, more recently, data have emerged showing that patients surviving an episode of CAP are at increased risk of death long after hospital discharge. In this descriptive review, we examine the current knowledge of long-term mortality and propose a hypothesis explaining the pathogenesis of long-term mortality in patients with CAP.

Current Literature

A total of 21 articles reporting long-term mortality data after hospitalizations for CAP were identified, with rates up to 10 or more years ranging between 17 and 50%, and up to 2-3 times higher than patients without a hospitalization for CAP [13–33]. After the initial review, we identified 15 articles reporting 1-year mortality rates. In Table 1 we summarized studies describing 1-year mortality in patients with CAP [13–19]. In Table 2 we summarized studies comparing 1-year mortality in patients with CAP to control groups [20–27]. Figure 1 represents the reported 1-year mortality for hospitalized patients with CAP for each study. These studies suggest that for all hospitalized patients with CAP, the 1-year mortality is approximately 30 to 35%. For hospitalized patients without CAP, the 1-year mortality is approximately 20 to 25%, whereas for those patients not hospitalized and not developing CAP the 1-year mortality was even lower, ranging between 1 and 5%. In hospitalized patients with CAP, there is a 10% increased risk for 1-year mortality in relation to hospitalized patients with other medical conditions. Follow-up periods vary among the different published studies evaluating long-term mortality. This, along with differences in the studied population, makes comparisons difficult. We believed that different exclusion criteria among the studies is the likely explanation for the wide range mortality reported in the studies.

One-Year Mortality in Patients with Community-Acquired Pneumonia

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Abstract

Pneumonia remains a common cause of morbidity and mortality in the US. Although, community-acquired pneumonia (CAP) has traditionally been considered an acute process, more recently, data have emerged showing that patients surviving an episode of CAP are at increased risk of death long after hospital discharge. In this descriptive review, we examine the current knowledge of long-term mortality and propose a hypothesis explaining the pathogenesis of long-term mortality in patients with CAP.
Table 1: Studies evaluating 1-year mortality after hospitalization due to CAP without a control group

| Author       | Study criteria | Study subjects | 1-year mortality |
|--------------|----------------|----------------|------------------|
| Waterer      | Prospective    | N= 109         | Not provided     |
| (2004)       |                |                | Estimated by age group |
|              | Subjects: age ≥ 18 years old hospitalized with CAP (Healthcare organization hospitals - Memphis, TN) |                | 18-40: 4%        |
|              | Pneumonia definition: acute illness (< 14 days of symptoms) with a positive chest image plus one criterion of Group A or two of Group B: |                | 41-60: 8%        |
|              | Group A        |                | 61-80: 20%       |
|              | ✓ Fever > 37.8°C or Hypothermia < 36°C ✓ Cough or sputum production |                | ≥81: 30%         |
|              | Group B        |                |                  |
|              | ✓ Dyspnea ✓ Physical findings of lung consolidation ✓ Leukocyte count > 12 x 10^9/L or < 4.5 x 10^9/L |                |                  |
|              | Exclusion criteria: AIDS, chemotherapy in the past 60 days, treatment with immunosuppressive medication, non-ambulatory nursing home patients, hospitalization within the prior 30 days. |                |                  |
| El Solh      | Prospective, observational | N= 301         | 10%              |
| (2006)       | Subjects: age ≥ 65 years old hospitalized with CAP (single center - Buffalo, NY) |                |                  |
|              | Pneumonia definition: positive chest image plus at least 2 of the following: |                |                  |
|              | ✓ Cough ✓ Dyspnea ✓ Chest pain ✓ Change in mental status |                |                  |
|              | and at least 1 of the following: |                |                  |
|              | ✓ Temperature ≥ 38°C or ≤ 36°C ✓ Leukocyte count (>10.0 x 10^9/L) or leukopenia (<3.5 x 10^9/L) and absence of evidence of a cause other than pneumonia |                |                  |
|              | Exclusion criteria: in home residents, hospitalization in the prior 90 days, aspiration, severe immunosuppression (solid organ transplantation, HIV/AIDS, steroid therapy > 10 mg/d for > 2 weeks), underlying active malignancy, or do not resuscitate order |                |                  |
| Johnstone    | Secondary analysis of prospective (implementation of a critical pathway for the management of CAP) | N= 3,284       | 28%              |
| (2008)       | Subjects: age ≥ 18 years old hospitalized with CAP (all 6 hospitals - Alberta, Canada) |                |                  |
|              | Pneumonia definition: positive chest image plus at least 2 of the following: |                |                  |
|              | ✓ Temperature > 38°C ✓ Chest pain ✓ Productive cough ✓ Crackles on auscultation ✓ Shortness of breath |                |                  |
|              | Exclusion criteria: immune deficiency (HV, use of > 10 mg/d of prednisone or other immunosuppressive agents, active treatment for cancer, history of organ transplantation, active TB, cystic fibrosis), shock, intubation or direct ICU admission, pregnant or breastfeeding women, alcohol addiction, chronic renal failure |                |                  |
| Cecere       | Prospective, observational | N= 457         | 15%              |
| (2010)       | Subjects: age ≥ 18 years old hospitalized with CAP (1 hospital - Washington, SA) |                | Estimated from survival analysis |
|              | Pneumonia definition: positive chest image plus either: |                |                  |
|              | ≥ 1 major criterion ✓ Cough ✓ Sputum production ✓ Fever (>37.9°C) or hypothermia (<35.0°C) ✓ Crackles on auscultation |                |                  |
|              | ≥ 2 minor criteria ✓ Pleuritic chest pain ✓ Dyspnea ✓ Altered mental status ✓ Abnormal chest examination findings ✓ Leukocytosis (white blood cell count >12,000 cells/mL), or left shift (>10% band forms) |                |                  |
|              | Exclusion criteria: transferred from another hospital, were hospitalized within 7 days before the index admission, were admitted for terminal care, or refused to give consent |                |                  |
| Kodali       | Prospective, observational | N= 153         | 5%               |
| (2014)       | Subjects: age ≥ 18 years old hospitalized with CAP (1 hospital – Kuopio, Finland) |                | Estimated from survival analysis |
|              | Pneumonia definition: acute febrile illness with a new radiographic shadowing (referencing BTS guidelines 2009) |                |                  |
|              | Exclusion criteria: severe pneumonia requiring ICU, refused to give consent, antibiotic treatment started in another institution |                |                  |
| Adamuz       | Prospective, observational | N= 1,284       | 7.2%             |
| (2014)       | Subjects: age ≥ 18 years old hospitalized with CAP (1 hospital - Barcelona, Spain) |                |                  |
|              | Pneumonia definition: not listed |                |                  |
|              | Exclusion criteria: neutropenia, immunoglobulin deficiencies, HIV infection, transplantation or splenectomy, receiving immunosuppressant and/or corticosteroid therapy >20 mg/day of prednisone or its equivalent |                |                  |
| Holter       | Prospective, observational | N= 259         | 9%               |
| (2016)       | Subjects: age ≥ 18 years old hospitalized with CAP (South-Eastern Norway) |                |                  |
|              | Pneumonia definition: positive chest image plus: |                |                  |
|              | ✓ Rectal temperature >38.0°C ✓ At least one of the following symptoms or signs: ✓ Cough (productive or non-productive) ✓ Dyspnea ✓ Chest pain ✓ Crackles or reduced respiratory sounds |                |                  |
|              | Exclusion criteria: non-infectious causes (pulmonary infarction, tumor or bronchiectasis) or if the patient had been hospitalized within the past 2 weeks. |                |                  |
### Table 2: Studies evaluating 1-year mortality after hospitalization due to CAP with a control group

| Author     | CAP cases                                                                 | Controls                                                                 | 1-year mortality |
|------------|---------------------------------------------------------------------------|---------------------------------------------------------------------------|------------------|
| Koivula    | N= 122                                                                   | N= 4,045                                                                  | CAP: 19% Controls: 4% |
| 1999       | Subjects: age ≥ 60 years old enrolled in a randomized, pneumococcal vaccination trial in Finland | Subjects enrolled in same randomized, pneumococcal vaccination trial in Finland who did not develop pneumonia |                  |
|            | **Pneumonia definition:** positive chest image plus one of the following: |                                                                            |                  |
|            | ✓ Temperature over 38.7°C and new or worsening cough PLUS one of the following: moist rales, dyspnea, tachypnea, cyanosis, pain in the chest or abdomen at respiration, purulent or blood stained sputum, acute deterioration of the general condition |                                                                            |                  |
|            | ✓ 2 of the following: temperature over 38.7°C, new/worsening cough plus moist rales, dyspnea, tachypnea, or cyanosis, pain in the chest or abdomen at respiration, purulent or blood stained sputum |                                                                            |                  |
|            | ✓ New or worsening cough and temperature over 38°C for more than 5 days.    |                                                                            |                  |
|            | **Exclusion criteria:** none                                               |                                                                            |                  |
| Kaplan     | N= 158,960                                                               | N= 794,333                                                                | CAP: 34% Controls: 25% |
| 2003       | Subjects: age ≥ 65 years old from the 1997 Medicare hospital discharge database | Five age, sex, and race matched from the same database who did not meet ICD-9 criteria |                  |
|            | **CAP definition:** ICD-9 codes 481, 482, 485, or 486 listed both at admission and discharge plus a pulmonary complaint on admission (ICD-9 518.81, 496, 786.09, 493.21, 507.0, 466.0, 786.3, 493.90, 786.3, 518.81) |                                                                            |                  |
|            | **Exclusion criteria:** transferred from other hospitals                  |                                                                            |                  |
| Carriere   | N= 43,642                                                                 | N= 1,950,997                                                              | CAP: 26% Controls: 5% |
| 2004       | Subjects: age ≥ 18 years old from 2 Canadian (Alberta Province) administrative health service databases | Alberta general population not hospitalized with pneumonia in 1994/1995 |                  |
|            | **CAP definition:** ICD-9 codes 480.0 - 487.8 (pneumonia) or 507.0 - 507.8 (aspiration pneumonia) |                                                                            |                  |
|            | **Exclusion criteria:** ICD-9 codes 484.1 – 484.7, non-Alberta residents, not treated in an Alberta acute care facility, previous hospitalization within 10 days |                                                                            |                  |
| Bordon     | N= 624                                                                   | N= 6,347                                                                  | CAP: 32% Controls: 20% |
| 2010       | Subjects: age ≥ 18 years old admitted to VA hospital                      | Hospitalized patients during same period due to medical conditions other than CAP |                  |
|            | **CAP definition:** positive chest image plus ≥1 of the following:        |                                                                            |                  |
|            | ✓ New or increased cough                                                   |                                                                            |                  |
|            | ✓ Abnormal serum leukocyte count                                           |                                                                            |                  |
|            | ✓ Abnormal temperature                                                     |                                                                            |                  |
|            | **Exclusion criteria:** none                                               |                                                                            |                  |
| Brouss     | N= 356                                                                   | N= 356                                                                    | CAP: 17% Controls: 4% |
| 2010       | Subjects: age ≥ 18 years old prospective cohort derived from two randomized clinical trials | Age and sex matched general population cohort                              |                  |
|            | **CAP definition:** positive chest image plus ≥2 of the following:        |                                                                            |                  |
|            | ✓ Cough                                                                   |                                                                            |                  |
|            | ✓ Sputum production                                                       |                                                                            |                  |
|            | ✓ Rectal temperature > 38°C or < 36.1°C                                     |                                                                            |                  |
|            | ✓ Auscultatory findings consistent with pneumonia                          |                                                                            |                  |
|            | ✓ Leukocytosis (>10³ white blood cells/litre or > 15% bands)              |                                                                            |                  |
|            | ✓ Positive culture of blood or pleural fluid                              |                                                                            |                  |
|            | ✓ C reactive protein more than three times the upper limit of normal       |                                                                            |                  |
|            | **Exclusion criteria:** mechanical ventilation in an intensive care unit, cystic fibrosis; a history of colonization with Gram-negative bacteria due to structural damage to the respiratory tract; life expectancy of less than one month because of underlying disease, infections other than pneumonia that needed antibiotic treatment, severe immunosuppression |                                                                            |                  |
| Sandvall   | N= 392                                                                   | N= not documented                                                         | CAP: 15% Controls: 1% |
| 2014       | Subjects: age ≥ 18 years old admitted to VA hospital with Streptococcal pneumonia | Expected 1-year survival of an average 63-year-old American male from the Human mortality database |                  |
|            | **CAP definition:** positive chest image plus ≥1 of the following:        |                                                                            |                  |
|            | ✓ Subjective fever                                                        |                                                                            |                  |
|            | ✓ Cough                                                                   |                                                                            |                  |
|            | ✓ Sputum production                                                       |                                                                            |                  |
|            | ✓ Pleuritic chest pain                                                    |                                                                            |                  |
|            | **Exclusion criteria:** none                                               |                                                                            |                  |
| Eurch      | N= 6,078                                                                 | N= 29,402                                                                 | CAP: 13% Controls: 5% |
| 2015       | Subjects: Age ≥ 18 years old enrolled in a clinical registry               | Age and sex matched                                                       |                  |
|            | **CAP definition:** positive chest image plus ≥2 of the following:        | Age at time of CAP case                                                   |                  |
|            | ✓ Cough                                                                   | Presenting to the hospital within the same month/year with a non-pneumonia diagnosis |                  |
|            | ✓ Pleuritic chest pain                                                    |                                                                            |                  |
|            | ✓ Shortness of air                                                        | No history of CAP in the prior year                                       |                  |
|            | ✓ Temperature >38°C                                                       |                                                                            |                  |
|            | ✓ Crackles on auscultation                                                 |                                                                            |                  |
|            | **Exclusion criteria:** immune deficiency, shock, mechanical ventilation on admission, pregnancy, breastfeeding, alcoholism, chronic renal disease. |                                                                            |                  |
| Mangen     | N= 582                                                                   | N= 1,123                                                                  | CAP: 8% Controls: 1% |
| 2017       | Subjects: age ≥ 65 years old enrolled in a pneumococcal vaccine study      | Age and sex matched                                                       |                  |
|            | **CAP definition:** positive chest image plus a positive PCV 13 vaccine-type-specific urinary antigen test or isolation of vaccine type S. pneumoniae from blood or another sterile site, plus the presence of ≥2 of the following: |                                                                            |                  |
|            | ✓ Cough                                                                   |                                                                            |                  |
|            | ✓ Production of purulent sputum or a change in the character of sputum    |                                                                            |                  |
|            | ✓ Temperature >38.0°C or <36.1°C                                          |                                                                            |                  |
|            | ✓ Auscultatory findings consistent with pneumonia including rales and/or evidence of pulmonary consolidation |                                                                            |                  |
|            | ✓ Leukocytosis (>10³ white blood cells/litre or >15% bands)              |                                                                            |                  |
|            | ✓ C-reactive protein >3 times the upper limit of normal                   |                                                                            |                  |
|            | ✓ Hypoxemia with a partial oxygen pressure (PO2) <60 mm Hg while the patient is breathing room air |                                                                            |                  |
|            | **Exclusion criteria:** previous vaccination with any pneumococcal vaccine, residence in long-term care facility, contraindication for 13vPcH, contraindication for influenza vaccines, use of investigational products in 30 days prior to study vaccine administration, history of severe adverse reaction associated with any vaccine component, immunodeficiency or immune suppression. |                                                                            |                  |
A hypothesis to explain long-term mortality

Chronic inflammation has been associated with aging and early death; a process described as “inflammaging” [34]. Persistent elevated levels of inflammatory cytokines have been documented in patients with CAP at time of hospital discharge. The increased long-term mortality after CAP may be mediated by an inflammatory response that persists after hospital discharge, adds to the inflammaging process, and accelerates the progression of medical comorbidities and early death [35, 36]. Months after hospital discharge, the primary cause of death may be cardiovascular disease or other underlying comorbidities. The prior episode of CAP would influence death by worsening the underlying comorbidity. Figure 2 is a schematic representation indicating the projected life expectancy of a 50-year-old patient who is hospitalized due to CAP (Figure 2, point 1). After the patient is discharged from the hospital, the projected life expectancy changes to line B and is considerably decreased (Figure 2, point 2). Mortality rates for patients with CAP have not significantly decreased since the 1950s [37]. Adjunctive therapies such as macrolides, statins, corticosteroids, and antiplalet agents have been studied in an attempt to improve short-term outcomes [38]. Despite the knowledge of higher mortality rates long after hospitalization for CAP, no studies evaluating the impact of adjunctive therapies on longterm outcomes have been conducted. It can be speculated that medications able to decrease chronic inflammation may reduce long term mortality in hospitalized patients with CAP.

Conclusions

Improving the clinical outcomes of hospitalized patients with CAP is of paramount importance for patients, as well as clinical investigators. The recent recognition of long-term mortality associated with CAP is opening a new frontier for clinical research in the field. We need studies to better define the underlying pathophysiology explaining the association of CAP with long-term mortality. Intervention to improve clinical outcomes in patients with CAP have frequently been tested in short term 30-day studies, since CAP was considered an acute problem without chronic implications. We need a new paradigm to design clinical trials to test interventions that may reduce long-term mortality.

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