STRATEGIES BEYOND ANTIBIOTICS: IMPACT ON MORTALITY

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Pulmonary, Critical Care and Sleep Medicine
Chong Hua Hospital, Cebu City
Be aware of the potential benefits of non-pharmacologic treatment strategies for community acquired pneumonia
During the ancient world, there were essentially only three diseases that affected breathing:

- Tuberculosis
- Asthma
- Pneumonia
"Peripneumonia, and pleuricic affections, are to be thus observed: If the fever be acute, and if there be pains on either side, or in both, and if expiration be if cough be present, and the sputa expectorated be of a blond or livid color, or likewise thin, frothy, and florid, or having any other character different from the common"

Hippocrates noted that death from pneumonia usually occurs on the seventh day.
Statistics from 1900 to 1937

- Pneumonia was annually either the number one or number two cause of death, with tuberculosis competing with it for the top spot.

- Statistics prior to 1900 are sparse, yet one might be right to assume pneumonia was consistently a leading cause of death since the beginning of human existence.
PNEUMONIA TREATMENT

• Bleeding
• If fever, the bowels were opened with clysters
• If pain, hot water in a bottle or bladder, a sponge of hot water, or cataplasm of linseed was applied to the hypochondrium
• Linctus containing galbanum and pine fruit in Attic Honey or...
• Sothernwood in oxymel
• Oppaponax (a bitter resin with a garlic taste) mixed in oxymel
• Drink of ptisan made from huskey barley and mixed with oxymel

Osler referred to pneumonia as the 'Captain of men and death."

He wrote, "It is *doubtful* whether the inhalation of oxygen in pneumonia is really beneficial. Personally, when called in consultation in a case, if I see the oxygen cylinder at the bedside I feel the prognosis to be extremely grave. It does sometimes seem to give transitory relief and to diminish the cyanosis. It is harmless, its exhibition is very simple, and the process need not be all that disturbing to the patient. The gas may be allowed to flow gently from the nozzle directly under the nostrils of the patient, or it may be administered every alternate 15 minutes through a mask."
Well, Mr. Green, the bad news is we’ve exhausted everything except ancient Chinese medicine. The good news is that if you’re gullible, it may have a placebo effect.
When I woke up just after dawn on September 28, 1928, I certainly didn't plan to revolutionize all medicine by discovering the world's first antibiotic, or bacteria killer," Fleming would later say, "But I suppose that was exactly what I did."
In the Philippines, pneumonia is fourth leading cause of mortality (2009) based on the Philippine Health Statistics from the Department of Health

In US, community acquired pneumonia

- Sixth leading cause of death
- Affects 5.6 million people per year
- Second-most common reason for hospitalization (2011)

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1 DOH. gov. ph
4 http://www.cdc.gov/nchs/fastats/pneumonia.htm
1996 meta-analysis of 127 studies that had over 33,000 patients

- The mortality rate ranged from 5.1 percent for combined ambulatory and hospitalized patients
- 13.6 percent in hospitalized patients
- 36.5 percent in patients admitted to the intensive care unit (ICU).


Pneumonia PORT (Patient Outcomes Research Team) study of 944 outpatients and 1343 inpatients

- Among outpatients, there were six deaths (0.6 percent), three of which were related to pneumonia.
- Among inpatients, the mortality rate was 8 percent; 76 percent of which were attributed to pneumonia.

INAPPROPRIATE INITIAL ANTIBIOTIC THERAPY AND HIGHER MORTALITY RATES

Mortality %

0 20 40 60 80 100


SPEED IS LIFE

Early diagnosis and timely administration of antibiotics are associated with improved outcomes in patients with CAP.

RECOMMENDATION

- Offer antibiotic therapy as soon as possible after diagnosis, and certainly within 4 hours, to all patients with community-acquired pneumonia admitted to hospital.

NICE Pneumonia Guidelines 2014

R. Phillip Dellinger, MD¹; Mitchell M. Levy, MD²; Andrew Rhodes, MB BS³; Djillali Annane, MD⁴; Herwig Gerlach, MD, PhD⁵; Steven M. Opal, MD⁶; Jonathan E. Sevransky, MD⁷; Charles L. Sprung, MD⁸; Ivor S. Douglas, MD⁹; Roman Jaeschke, MD¹⁰; Tiffany M. Osborn, MD, MPH¹¹; Mark E. Nunnally, MD¹²; Sean R. Townsend, MD¹³; Konrad Reinhart, MD¹⁴; Ruth M. Kleinpell, PhD, RN-CS¹⁵; Derek C. Angus, MD, MPH¹⁶; Clifford S. Deutschman, MD, MS¹⁷; Flavia R. Machado, MD, PhD¹⁸; Gordon D. Rubenfeld, MD¹⁹; Steven A. Webb, MB BS, PhD²⁰; Richard J. Beale, MB BS²¹; Jean-Louis Vincent, MD, PhD²²; Rui Moreno, MD, PhD²³; and the Surviving Sepsis Campaign Guidelines Committee including the Pediatric Subgroup*
D. Antimicrobial Therapy

1. Administration of effective intravenous antimicrobials within the first hour of recognition of septic shock (grade 1B) and severe sepsis without septic shock (grade 1C) as the goal of therapy.
FACTORS INVOLVED IN OPTIMAL INITIAL ANTIBIOTIC THERAPY

- Pathogen coverage
- Timely initiation
- Correct dose
- Correct route

Increased survival
<table>
<thead>
<tr>
<th>Evidence level</th>
<th>Definition</th>
<th>Guideline statement grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ia</td>
<td>A good recent systematic review of studies designed to answer the question of interest</td>
<td>A+</td>
</tr>
<tr>
<td>Ib</td>
<td>One or more rigorous studies designed to answer the question, but not formally combined</td>
<td>A−</td>
</tr>
<tr>
<td>II</td>
<td>One or more prospective clinical studies which illuminate, but do not rigorously answer, the question</td>
<td>B+</td>
</tr>
<tr>
<td>III</td>
<td>One or more retrospective clinical studies which illuminate, but do not rigorously answer, the question</td>
<td>B−</td>
</tr>
<tr>
<td>IVa</td>
<td>Formal combination of expert views</td>
<td>C</td>
</tr>
<tr>
<td>IVb</td>
<td>Other information</td>
<td>D</td>
</tr>
</tbody>
</table>

A fuller description is given in Section 1 and Appendices 1–4.
Patients with suspected CAP should be advised to rest, to drink plenty of fluids and not to smoke. [D]

Pleuritic pain should be relieved using simple analgesia such as paracetamol. [D]

Pulse oximetry, with appropriate training, should be available to general practitioners and others responsible for the assessment of patients in the out-of-hours setting for the assessment of severity and oxygen requirement in patients with CAP and other acute respiratory illnesses. [D]
All patients should receive appropriate oxygen therapy with monitoring of oxygen saturations and inspired oxygen concentration with the aim to maintain arterial oxygen tension (PaO\(_2\)) at >8 kPa and oxygen saturation (SpO\(_2\)) 94–98%. High concentrations of oxygen can safely be given in patients who are not at risk of hypercapnic respiratory failure. [D]

Oxygen therapy in patients at risk of hypercapnic respiratory failure complicated by ventilatory failure should be guided by repeated arterial blood gas measurements. [C]

NICE Pneumonia Guidelines 2009, Thorax 2009;64(Suppl III)
Patients should be assessed for volume depletion and may require intravenous **fluids**. [C]

**Prophylaxis** of venous thromboembolism with low molecular weight heparins should be considered for all patients who are not fully mobile. [A+]

**Nutritional support** should be given in prolonged illness.[C]

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**GENERAL MANAGEMENT STRATEGY**

NICE Pneumonia Guidelines 2009, Thorax 2009;64(Suppl III)
## EARLY ENTERAL FEEDING META-ANALYSIS

<table>
<thead>
<tr>
<th>Author/Journal</th>
<th>Study Parameters</th>
<th>Study Design</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Marik. <em>CCM</em>. 2001.</td>
<td>Feeding &lt; or &gt;36 hr</td>
<td>15 studies</td>
<td>↓ Infections</td>
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<tr>
<td></td>
<td></td>
<td>753 patients</td>
<td>↓ LOS*</td>
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<tr>
<td>Lewis. <em>BMJ</em>. 2001.</td>
<td>NPO vs &lt;24 hr</td>
<td>11 studies</td>
<td>↓ Infections</td>
</tr>
<tr>
<td></td>
<td></td>
<td>837 patients</td>
<td>↓ LOS</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>↑ Vomiting risk</td>
</tr>
<tr>
<td>Heyland. <em>JPEN</em>. 2003.</td>
<td>&lt;24 to 48 hr</td>
<td>8 studies</td>
<td>Trend to ↓ infections and</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>mortality</td>
</tr>
<tr>
<td>Lewis SJ <em>J GI Surg</em> 2008</td>
<td>&lt;24 hr</td>
<td>13 studies</td>
<td>Decrease mortality</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1173 patients</td>
<td></td>
</tr>
<tr>
<td>Doig GS <em>Int Care Med</em> 2009</td>
<td>&lt;24 hr</td>
<td>5 studies</td>
<td>Decrease infection and</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>mortality</td>
</tr>
</tbody>
</table>
HOW MUCH IS ENOUGH TO REAP THE BENEFITS OF EN?

- **Immune benefit:**
  - 15 – 30% calories enterally

- **Visceral blood flow benefit:**
  - 10 – 20% calories enterally

- **Maintenance of gut mass and gut barrier function**
  - 50 - 60% requirements early post injury (24 - 48 hours)

*(Cresci & Martindale 2001)*
Medical condition permitting, patients admitted to hospital with uncomplicated CAP should sit out of bed for at least **20 min** within the first **24 h** and mobility should be increased each subsequent day of hospitalization. [A2]

Patients admitted with uncomplicated pneumonia should not be treated with traditional airway clearance techniques routinely. [B+]

Patients should be offered advice regarding expectoration if there is sputum present. [D]

Airway clearance techniques should be considered if the patient has sputum and difficulty with expectoration or in the event of a pre-existing lung condition. [D]
Chest physiotherapy for pneumonia in adults (Review)

Figure 3. Forest plot of comparison: 1 Chest physiotherapy plus routine treatment versus routine treatment alone, outcome: 1.1 Mortality.

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Chest physiotherapy</th>
<th>No physiotherapy</th>
<th>Risk Ratio M-H, Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Britten 1985</td>
<td>1</td>
<td>1</td>
<td>1.06 [0.07, 10.68]</td>
</tr>
<tr>
<td>Graham 1979</td>
<td>1</td>
<td>1</td>
<td>1.00 [0.07, 15.10]</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td>110</td>
<td>115</td>
<td>1.03 [0.15, 7.13]</td>
</tr>
</tbody>
</table>

Total events: 2

Heterogeneity: Chi² = 0.00, df = 1 (P = 0.99); P = 0%
Test for overall effect: Z = 0.03 (P = 0.98)
Granulocyte colony stimulating factor is not routinely recommended as an adjunct to antibiotics. [A+]

NICE Pneumonia Guidelines 2009, Thorax 2009;64(Suppl III)
Granulocyte-Colony Stimulating Factor (G-CSF) as an adjunct to antibiotics in the treatment of pneumonia in adults

(Review)

Cheng AC, Stephens DP, Currie BJ
Six studies with a total of 2018 people were identified.

GCSF use appeared to be safe with no increase in the incidence of total serious adverse events (pooled odds ratio (OR) 0.91; 95% confidence interval (CI): 0.73 to 1.14) or organ dysfunction.

However, the use of G-CSF was not associated with improved 28-day mortality (pooled OR 0.81; 95% CI: 0.52 to 1.27).
Early thoracocentesis is indicated for all patients with a parapneumonic effusion. [D]

Those found to have an empyema or clear pleural fluid with pH 7.2 should have early and effective pleural fluid drainage. [C]

NICE Pneumonia Guidelines 2009, Thorax 2009;64(Suppl III)
All patients aged 65 years or at risk of invasive pneumococcal disease who are admitted with CAP and who have not previously received pneumococcal vaccine should receive 23-valent pneumococcal polysaccharide vaccine (23-PPV) at convalescence in line with the Department of Health guidelines. [C]

Smoking cessation advice should be offered to all patients with CAP who are current smokers according to smoking cessation guidelines issued by the Health Education Authority. [B+]

NICE Pneumonia Guidelines 2009, Thorax 2009;64(Suppl III)
NEITHER NON-INVASIVE VENTILATION (NIV) NOR CONTINUOUS POSITIVE AIRWAYS PRESSURE (CPAP) SUPPORT IS ROUTINELY INDICATED IN THE MANAGEMENT OF PATIENTS WITH RESPIRATORY FAILURE DUE TO CAP. [A2]

IF A TRIAL OF NON-INVASIVE SUPPORT IS CONSIDERED INDICATED IN CAP, IT MUST ONLY BE CONDUCTED IN A CRITICAL CARE AREA WHERE IMMEDIATE EXPERTISE IS AVAILABLE TO ENABLE A RAPID TRANSITION TO INVASIVE VENTILATION. [D]

STEROIDS ARE NOT RECOMMENDED IN THE ROUTINE TREATMENT OF HIGH SEVERITY CAP. [A+]

NICE PNEUMONIA GUIDELINES 2009, THORAX 2009;64(SUPPL III)
Pneumonia

Diagnosis and management of community- and hospital-acquired pneumonia in adults

Clinical guideline <...>

Methods, evidence and recommendations

June 2014

Draft for Consultation

Commissioned by the National Institute for Health and Care Excellence
STEROIDS AND PNEUMONIA

- Symptoms experienced and illness features that are measured in pneumonia are caused by inflammation rather than the causative agents.
- Even when appropriate antibiotic therapy is administered and the causative bacteria killed, not only can the illness and its symptoms continue for some time, but in severe cases death may yet ensue.
- Can steroids alter the symptoms, illness duration and outcome through suppression of the inflammatory response?
RANDOMIZED TRIALS


McHardy VU, Schonell ME. Ampicillin dosage and use of prednisolone in treatment of pneumonia: co-operative controlled trial. BMJ. 1972; 4(5840):569-573


RANDOMIZED TRIALS

- Sabry NA, Omar EE-D. Corticosteroids and ICU Course of Community Acquired Pneumonia in Egyptian Settings. Pharmacology and Pharmacy. 2011; 2(2):73-81

## STEROIDS AND PNEUMONIA

<table>
<thead>
<tr>
<th>STUDIES</th>
<th>NUMBER OF PATIENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Confalonieri 2005</td>
<td>N = 48; CAP, ICU setting - Italy</td>
</tr>
<tr>
<td>Fernandez-Serrano 2011</td>
<td>N = 56; CAP</td>
</tr>
<tr>
<td>Marik 1993</td>
<td>N = 30; CAP, ICU setting - South Africa</td>
</tr>
<tr>
<td>McHardy 1972</td>
<td>N = 126; CAP</td>
</tr>
<tr>
<td>Meijvis 2011</td>
<td>N = 304; CAP</td>
</tr>
<tr>
<td>Mikami 2007</td>
<td>N = 31; CAP</td>
</tr>
<tr>
<td>Sabry 2011</td>
<td>N = 80; CAP, ICU setting - Egypt</td>
</tr>
<tr>
<td>Snijders 2010</td>
<td>N = 123; CAP</td>
</tr>
</tbody>
</table>
In all settings, the evidence from the randomised trials showed no clinical benefit in mortality rates for the group of patients on glucocorticosteroid treatment plus antibiotic therapy compared with those on antibiotic treatment alone.
<table>
<thead>
<tr>
<th>Quality assessment</th>
<th></th>
<th>No of patients</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No of studies</td>
<td>Design</td>
<td>Risk of bias</td>
<td>Inconsistency</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>randomised trials</td>
<td>very serious</td>
<td>no serious</td>
</tr>
<tr>
<td>1</td>
<td>randomised trials</td>
<td>serious⁵</td>
<td>no serious</td>
</tr>
</tbody>
</table>

Mortality up to 8 days (ITU setting) [Confalonieri 2005, Marik 1993, Sabry 2011] (sensitivity analysis)

Mortality at 60 days (ITU setting) [Confalonieri 2005]
In an ICU setting, the evidence suggested reduced mortality in patients treated with a glucocorticosteroid.

There also appeared to be a reduced dependence on mechanical ventilation and a reduced incidence of some complications (MODS).

Other outcomes, including clinical cure, length of hospital stay and other complications, were not reported in ICU-based studies and showed no difference between the 2 intervention arms for patients treated outside an ICU setting.

Large, clinically important increase in hyperglycaemia with glucocorticosteroid treatment
Do not routinely offer a glucocorticosteroid to patients with community acquired pneumonia unless they have other conditions for which glucocorticosteroid treatment is indicated.

- Much of the evidence was of low or very low quality by GRADE criteria due to methodological flaws of the included studies, and that the quality of evidence was lowest for the most critical outcomes, including mortality.
- Concern regarding the reliability of the evidence of mortality benefit in the ICU setting. Only 3 studies with a small number of patients, conducted in different countries at different times, and using different glucocorticosteroid doses and regimes, contributed to the mortality evidence in an ICU setting.
  - The different treatment groups were not well matched; for example, a larger proportion of the placebo groups required ventilatory support prior to randomization.

NICE Pneumonia Guidelines 2014
There are 3 on-going trials examining the use of glucocorticosteroid treatment in CAP. These studies are aiming to include a large number of patients in comparison with the currently available evidence, and may hopefully contribute to strengthening the evidence base in this topic.

NICE Pneumonia Guidelines 2014
In adults with community-acquired pneumonia or hospital-acquired pneumonia managed in hospital, what is the clinical and cost effectiveness of non-invasive ventilation compared with continuous positive airways pressure or usual care?

NICE Pneumonia Guidelines 2014
NIV AND CPAP

- No studies were found comparing NIV (Bi-level CPAP) to CPAP or usual care.
- Two RCTs comparing CPAP to usual care were identified.
Randomised 56 patients with CAP and indicators of a more severe illness (respiratory rate of over 30, and respiratory acidosis) who were treated in ICU to receive either CPAP or usual care.

Population: patients with and without COPD who were analyzed by post-hoc subgroup analysis.

No overall difference in mortality between treatment groups.

There was an apparent reduction in need for intubation, duration of intubation and length of stay in ICU in patients treated with CPAP, though this effect was heavily weighted by a large effect seen in the COPD subgroup, with little difference seen in those without COPD.

Duration of hospital stay was shorter with CPAP in patients with CAP with COPD, but longer in patients with CAP without COPD.

Randomised 47 patients with CAP who were less sick (respiratory rate < 35, excluded patients with respiratory acidosis) who were treated outside ICU with CPAP or usual care.

Follow-up was for 48 hours only, with no deaths or intubations reported.

Patients achieved a PaO2/FiO2 ratio of ≥ 315 (a surrogate for clinical improvement) more quickly with CPAP than with usual care.
Evidence was of moderate to very low quality by GRADE criteria, with the majority of evidence being of low or very low quality.

The GDG noted that the number of patients included in the available studies was small, with a degree of imprecision around many of the results.

In the absence of any evidence regarding NIV in CAP the GDG could not make a recommendation regarding its use, either positive or negative, and prioritized a research recommendation in this area.
Over-the-counter (OTC) medications to reduce cough as an adjunct to antibiotics for acute pneumonia in children and adults (Review)

Chang CC, Cheng AC, Chang AB
Four studies with a total of 224 participants that were suitable for inclusion
- one was performed exclusively in children
- three in adolescents or adults.

Data could only be obtained from two studies; both studies used mucolytics (ambroxol and bromhexine) in conjunction with antibiotics.

Combining these two studies, the rate of cure or improvement in cough of people who received mucolytics was similar to those who did not.
No reported increased adverse events in the treatment group.

There are no studies of other common OTC medications such as antihistamines and antitussives.

Thus, there is insufficient evidence to draw any definitive conclusions on the role of OTC medications taken as an additional treatment for cough associated with acute pneumonia.

Mucolytics may be beneficial but the lack of consistent evidence precludes recommending the routine use of mucolytics as an addition in the treatment of troublesome cough associated with pneumonia in children or adults.

The evidence is current to January 2014.
Initial appropriate antibiotic therapy for CAP is the single most important factor in survival.

Adjunctive measures that work:
- Early Nutrition
- Bed rest, fluids, oxygen
- DVT prophylaxis for immobilized patients

Adjunctive measures that does not work:
- GCSF
- Activated protein C
- Immunoglobulin infusion
- Chest Physiotherapy for all CAP

Adjunctive measures that need more studies:
- Steroids
- NIV
- Over the Counter Medications
- Statins
GREETINGS FROM PCCP CEBU
STATINS

- Used to lower cholesterol levels for prevention of cardiovascular disease.
- Exert anti-inflammatory and immunomodulating effects
- Reported to counteract the deleterious effects of sepsis on coagulation
- May directly inhibit pathogenic microorganisms
STATINS IN PNEUMONIA

META-ANALYSIS

  - 20 studies, including only 1 randomized controlled trial, and found lower mortality (including pneumonia-related mortality) with statin use, defined as taking any statin for any reason
  - Suggested efficacy of statins for treating and preventing infections
  - no evidence of preventive efficacy
Effect of Statin Therapy on Mortality in Patients With Ventilator-Associated Pneumonia
A Randomized Clinical Trial
Randomized, placebo-controlled, double-blind, parallel-group, multicenter trial performed in 26 intensive care units in France from January 2010 to March 2013.

For power to detect an 8% absolute reduction in the day-28 mortality rate, we planned to enroll 1002 patients with suspected VAP.

The study was stopped for futility at the first scheduled interim analysis after enrollment of 300 patients.

JAMA. 2013;310(16):1692-1700
<table>
<thead>
<tr>
<th>Outcome</th>
<th>No. (%) [95% CI]</th>
<th>Between-Group Difference, % (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Simvastatin (n = 146)</td>
<td>Placebo (n = 138)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mortality</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Day 28 (primary outcome)</td>
<td>31 (21) [15 to 29]</td>
<td>21 (15) [10 to 22]</td>
<td>6 (-3 to 15)</td>
</tr>
<tr>
<td>Day 14</td>
<td>22 (15) [10 to 22]</td>
<td>16 (12) [7 to 18]</td>
<td>3 (-5 to 11)</td>
</tr>
<tr>
<td>ICU</td>
<td>38 (26) [20 to 34]</td>
<td>30 (22) [16 to 29]</td>
<td>4 (-5 to 14)</td>
</tr>
<tr>
<td>Hospital</td>
<td>43 (30) [23 to 37]</td>
<td>38 (28) [21 to 36]</td>
<td>2 (-8 to 12)</td>
</tr>
<tr>
<td></td>
<td></td>
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<tr>
<td>No. of ventilator-free days, median (IQR)</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Day 1 to day 28</td>
<td>10 (0 to 21)</td>
<td>8 (0 to 20)</td>
<td>.85</td>
</tr>
<tr>
<td>Day 1 to day 90</td>
<td>70 (0 to 82)</td>
<td>69 (32 to 81)</td>
<td>.71</td>
</tr>
<tr>
<td>No. of days outside ICU from day 1 to day 28, median (IQR)</td>
<td>3 (0 to 16)</td>
<td>0 (0 to 14)</td>
<td>.35</td>
</tr>
<tr>
<td>ARDS</td>
<td>17 (12) [7 to 18]</td>
<td>12 (9) [5 to 15]</td>
<td>3 (-4 to 10)</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>2 (1) [0 to 5]</td>
<td>1 (1) [0 to 4]</td>
<td>0 (-3 to 4)</td>
</tr>
<tr>
<td>Myocardial ischemia</td>
<td>1 (1) [0 to 4]</td>
<td>1 (1) [0 to 4]</td>
<td>0 (-3 to 3)</td>
</tr>
<tr>
<td>Time from randomization among patients alive at hospital discharge, median (IQR), (d)</td>
<td></td>
<td></td>
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<tr>
<td>To discontinuation of mechanical ventilation</td>
<td>12 (7 to 24)</td>
<td>14 (7 to 29)</td>
<td>.40</td>
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<tr>
<td>To ICU discharge</td>
<td>18 (10 to 31)</td>
<td>18 (12 to 33)</td>
<td>.29</td>
</tr>
<tr>
<td>To hospital discharge</td>
<td>37 (21 to 59)</td>
<td>35 (22 to 62)</td>
<td>.63</td>
</tr>
</tbody>
</table>
Figure 2. Proportions of Nonsurvivors in the Simvastatin and Placebo Groups

- **Simvastatin**
- **Placebo**

<table>
<thead>
<tr>
<th>Time From Randomization, d</th>
<th>No. at risk Simvastatin</th>
<th>No. at risk Placebo</th>
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</thead>
<tbody>
<tr>
<td>0</td>
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<td>138</td>
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<td>24</td>
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<td>28</td>
<td>115</td>
<td>117</td>
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</table>
In adults with suspected VAP, adjunctive simvastatin therapy compared with placebo did not improve day-28 survival. These findings do not support the use of statins with the goal of improving VAP outcomes.
In the 1960s and 1970s physicians noted the high incidence of pneumonia after operations -- particularly abdominal surgeries -- despite the use of antibiotics. Similar observations were noted among patients taking sedatives or pain relievers such as morphine.

Further study helped researchers determine the reason was because due to pain, or due to the sedatives, these patients weren't taking deep enough breaths, and weren't adequately coughing. This helped to create a breeding ground in the lungs for certain bacteria. Post operative pneumonia was learned to complicate treatment, prolong hospital stays, and even cause death.

To treat this, the incentive spirometer was invented. The goal of this device was to encourage post operative patients to take deep breaths followed by a breath hold and a good cough. It was also recommended that post operative patient get out of bed and start moving as soon as possible after surgery to prevent pneumonia.

So the incidence of pneumonia took a sharp decline, and deaths likewise declined. When a pneumonia vaccine hit the market in 1977 pneumonia rates declined a little more. By 2000 a pneumonia vaccine became available for children, and this helped decline pneumonia deaths to its current level as the sixth leading cause of death.