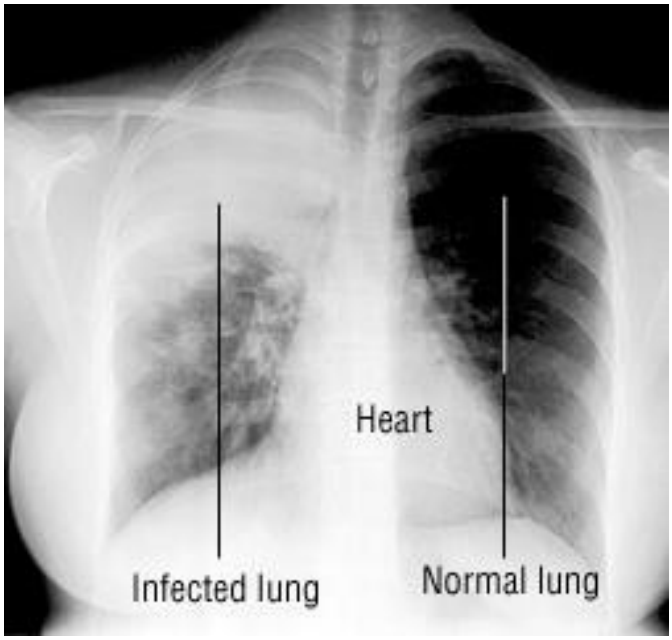
Steroids in Community-Acquired Pneumonia: Should the Idea be "Suppressed" or Standard of Care?



http://www.drugs.com/health-guide/pneumonia.html[1]

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Learning Objectives:

1. Describe the rationale for steroid use in community-acquired pneumonia (CAP)
2. Analyze recent literature regarding steroid use in CAP patients
3. Evaluate steroid use in CAP patients based on severity of illness and patient specific factors

Background:

A. Definitions and Diagnostics:

a) Definition of community-acquired pneumonia (CAP):

i. Acute infection of the pulmonary parenchyma associated with symptoms of an infection accompanied by an acute infiltrate on a chest radiograph or auscultatory findings consistent with pneumonia such as altered breath sounds or localized rales[2]

ii. Occurs in a non-hospitalized patient or ≤ 48 hours of hospitalization.[2]

iii. Refer to Appendix Table 1 for the definitions of other types of pneumonia.[3]

b) Signs and Symptoms[4,5]:

i. Dyspnea, cough, increased sputum production, chest pain, and fever.

B. Epidemiology:

a) Prevalence:

i. More than 5 million patients develop CAP annually in the United States.[6]

ii. More than 10 million visits to physicians and 64 million days of restricted activity in the United States annually.[7]

b) Hospitalizations[6-8]:

i. Annually, in the United States, 1.1 million patients hospitalized for pneumonia

ii. Approximately 600,000 patients hospitalized for CAP.

c) Mortality:

i. World-wide, lower respiratory tract infections account for 3.1 million deaths.[9]

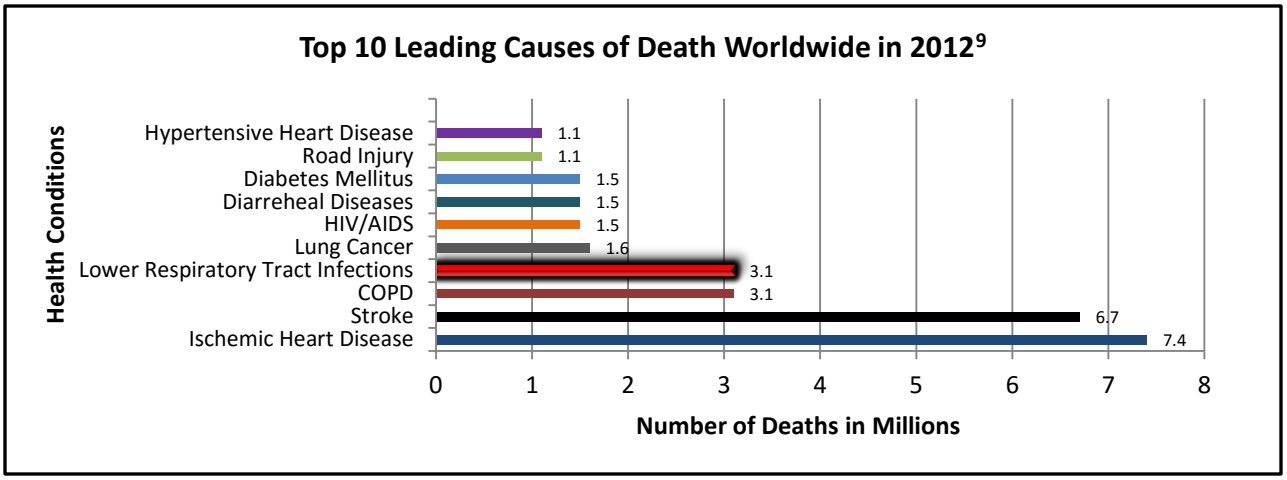
ii. Third largest cause of mortality.[9] (See Figure 1.)

iii. Despite current treatment, death rates from lower respiratory tract infections have remained stable for past decade.[9,10]

iv. In the United States, pneumonia and influenza together are the ninth leading cause of death.[11]

v. Account for approximately 50,000 deaths annually.[11]

Figure 1: Leading Causes of Death, Reported in Millions



d) Health-Care Costs:

i. In the United States, approximately $10 billion spent on treatment of patients with CAP.

ii. 92% of these costs are attributed to hospitalizations.[12]

C. Common Pathogens:[10]

Table 1: Common CAP Pathogens[10]		
Outpatient	**Inpatient (Non-ICU)**	**Inpatient ICU**
S. pneumoniae *M. pneumoniae* *H. influenzae* *C. pneumoniae* Respiratory viruses*	*S. pneumoniae* *M. pneumoniae* *H. influenzae* *C. pneumoniae* Respiratory viruses* *Legionella* species Aspiration	*S. pneumonia* *H. influenzae* *Legionella* species Gram-negative bacilli *S. aureus*
* Influenza A and B, adenovirus, respiratory syncytial virus, and parainfluenza.		

D. Current Empiric Treatment:

Table 2: CAP Empiric Treatment[10]		
Site of Care	**Risk Factors/Allergy**	**Antibiotic Options**
Outpatient	Healthy/No Recent Antibiotic Use*	macrolide or doxycycline
	Comorbidities§/Recent Antibiotic Use*	anti-pneumococcal FQ° or beta-lactam‡ + macrolide$^{\Delta}$
Inpatient (Non-ICU)		anti-pneumococcal FQ° or beta-lactam¤ + macrolide$^{\Delta}$
Inpatient (ICU)		beta-lactam$ + azithromycin or anti-pneumococcal FQ°
	Penicillin Allergy	aztreonam + anti-pneumococcal FQ°
	Concern for *Pseudomonas*	Anti-pseudomonal beta-lactam% + aminoglycoside + azithromycin OR Anti-pseudomonal beta-lactam% + ciprofloxacin or levofloxacin OR Anti-pseudomonal beta-lactam% + aminoglycoside + ciprofloxacin or levofloxacin
	Concern for MRSA	ADD vancomycin or linezolid

* antibiotic use within 3 months
§ chronic heart, lung, liver or renal disease; diabetes mellitus; alcoholism; malignancies; asplenia; immunosuppressing conditions or drugs
° anti-pneumococcal fluoroquinolone: moxifloxacin, gemifloxacin or levofloxacin
‡ preferred beta-lactams: amoxicillin or amoxicillin-clavulanate; alternatives: ceftriaxone, cefpodoxime, cefuroxime
Δ doxycycline can be used as an alternative to a macrolide
¤ preferred beta-lactams: cefotaxime, ceftriaxone, and ampicillin
$ preferred beta-lactams: cefotaxime, ceftriaxone, or ampicillin-sulbactam
% anti-pseudomonal beta-lactam: piperacillin-tazobactam, cefepime, imipenem, or meropenem

E. Understanding Glucocorticoids Role in Pneumonia:

a) Inflammatory Process in Pneumonia:[13]

i. Cytokines play an essential role in clearing pathogens, repairing lung tissue, and modulating inflammatory response.

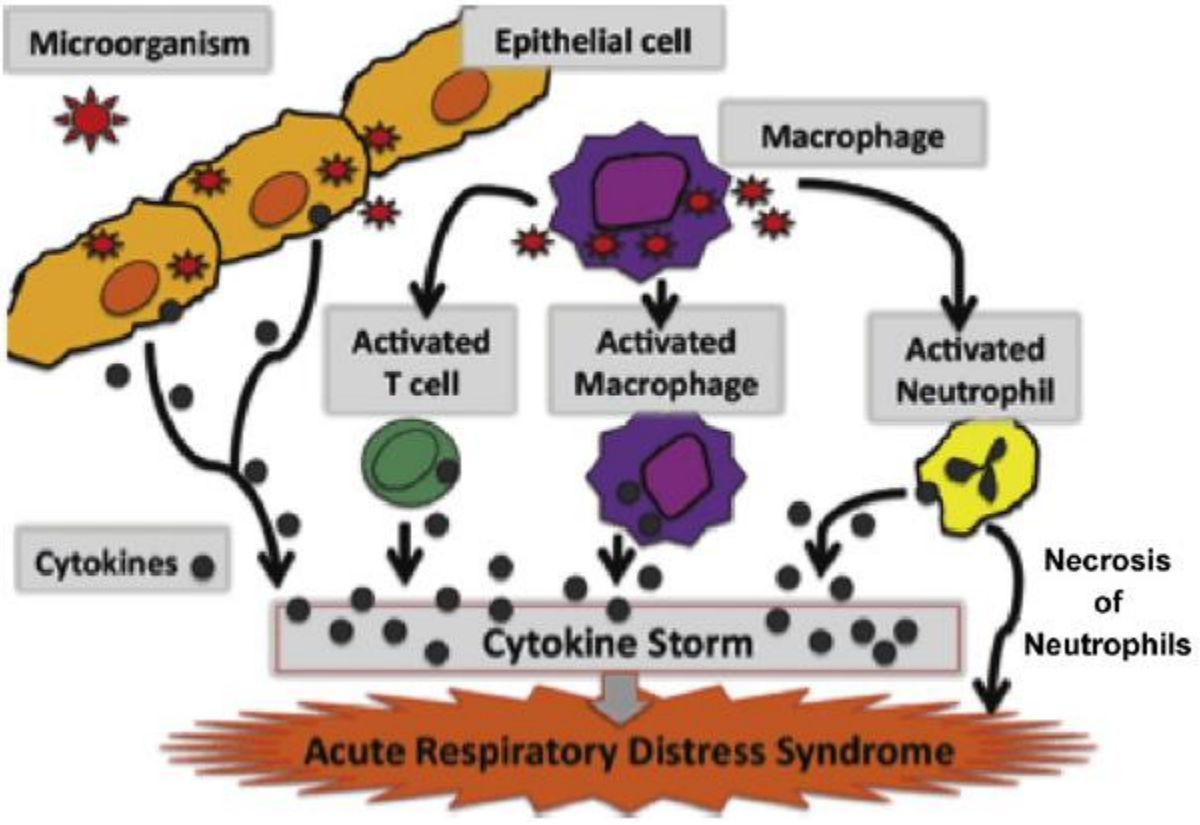
ii. During early infection, alveolar macrophages produce pro-inflammatory cytokines and chemokines such as: tumor necrosis factor-alpha (TNF-a), interleukin (IL)-1, IL-6, IL-8, IL-12, and interferon gamma (IFN-γ).
   1. Pro-inflammatory cytokines responsible for recruiting neutrophils to affected lung tissue.

iii. Neutrophils are then activated and able to phagocytize and kill ingested bacteria by producing particles such as toxic oxygen radicals and bactericidal enzymes.
   1. Neutrophils also recruit monocytes, dendritic cells, and T-cells to site of infection.

iv. Once infection is controlled, anti-inflammatory cytokines, such as IL-10 and IL-4, will function to restore homeostasis, modulate neutrophil apoptosis, and inhibit pro-inflammatory cytokine production.

v. If this process fails, a cytokine storm results in deleterious inflammation leading to pulmonary endothelial barrier disruption and poor clinical outcomes such as protein rich fluid extravasation, lung edema, and acute respiratory distress syndrome (ARDS)[14]. (See Figure 2)

Figure 2:
Proposed Mechanism for Cytokine Storm and Poor Clinical Outcomes in CAP Patients with Deleterious Inflammation[13]



B. Inflammatory Response Supporting Literature:

Table 3: Inflammatory Response Supporting Literature:					
Study	Objective	Design	Population	Results	Take-Away
Yende et al[15]	To determine if elevated circulatory markers at hospital discharge in CAP patients are associated with poor outcomes	Observational, prospective, multi-center cohort	N=1,799 1,512 (87%) of patients' vital signs returned to normal	IL-6 levels: Survivors vs. non-survivors at 100 days: 6.6pg/mL vs. 12.9 pg/mL; p<0.001 IL-10 levels: Survivors vs. non-survivors at 6 months: 1.1 pg/mL vs. 2 pg/mL; p<0.001	Despite clinical recovery, many patients with CAP have sustained elevations in inflammatory markers that are associated with an increased risk of death.
Fernandez-Serrano et al[16]	To determine the changes of cytokine concentrations during pneumonia and analyze the relationship between cytokines and etiology, severity, and outcome of infection	Prospective laboratory study	N=38; severe CAP, extensive radiographic consolidations, and respiratory failure	Lower IL-6 values by day 2: non-ICU patients vs. ICU patients; p=0.001 Lower IL-10 values by day 3: non-ICU vs. ICU patients; p=0.003 Higher TNF-α, IL-8, IL-10 on day 1 for ventilated vs. non-ventilated; p=0.05, p=0.04, p=0.04, respectively	Mechanical ventilation and severity of illness were associated with higher levels of cytokines compared to non-ventilated and lower severity of illness

C. Glucocorticoid Rationale:[13,17-18]

a) Glucocorticoid mechanism of action**:** inhibit various cytokines including the cytokines involved in pneumonia such as: IL-1, IL-2, IL-3, IL-4, IL-5, IL-6, IL-8, IL-12, INF-γ, and TNF-α.
b) Cost**:** inexpensive
c) Therapeutic drug monitoring: not necessary
d) Corticosteroids mimic the body's natural stress response.

D. Controversy

a) Clinical Questions:
i. What are the benefits of steroid use in CAP?
ii. What population, if any, benefits the most from steroid use in CAP?
iii. What are the risks associated with the use of steroids in CAP?

Observational Studies:

Table 4: Observational Studies				
Study	Design	Population	Results	Take-Away
Monton et al[19]	Pilot study	N=20; mechanically ventilated pneumonia; ICU	Higher serum IL-6 in non-steroid group vs. steroid group; p=0.03	Steroids decreased systemic and lung inflammatory responses in mechanically ventilated patients w/ severe pneumonia receiving antibiotics.
			Higher serum C-reactive protein non-steroid group vs. steroid group; p=0.04	
			Higher bronchoalveolar lavage (BAL) fluid TNF-α: non-steroid group vs. steroid group; p=0.05	
			Higher BAL fluid neutrophil count non-steroid group vs. steroid group; p=0.03	
Garcia-Vidal et al[20]	Retrospective, observational	N=308; severe CAP Pneumonia Severity Index (PSI) classes IV/ V (See Appendix Table 2)[21]	Steroid group: decreased mortality: odds ratio: 0.287; 95% CI: 0.113-0.732	Mortality decreased in severe CAP patients receiving antibiotics and steroids.
Tagami et al[22]	Multi-center, observational study	N=6925; severe CAP; mechanically ventilated	28 day mortality in septic shock patients: steroids vs. no steroids: 25.3% vs. 32.6%; p=0.01	Low-dose corticosteroid use may be associated with decreased 28-day mortality in patients w/ septic shock complicating CAP.
			28 day mortality in non-shock pts: steroids vs. no steroids: 17.7% vs. 15.6%;p=0.22	
Polverino et al[23]	Observational	N=3257 CAP patients	Mortality: 6% vs. 7%;p=0.46	Steroids did not influence mortality or clinical stability. Steroid administration was associated with prolonged length of stay.
			Length of hospital stay: steroid vs. no steroid: 9 vs. 6 days; p<0.01	
			Clinical stability: 4 vs 5 days; p=0.11	

Recent Randomized, Controlled Trials:

Table 5: 2015 Torres, et al.[24]
Effect of Corticosteroids on Treatment Failure Among Hospitalized Patients with Severe Community-Acquired Pneumonia and High Inflammatory Response: A Randomized Clinical Trial

Objective	To assess the effect of corticosteroids in patients with severe CAP and high associated inflammatory response.
Design	Multi-center at 3 Spanish institutions, randomized, double-blind, placebo-controlled. Patients were recruited and followed from June 2004 – February 2012.
Inclusion	• Age ≥ 18 • Clinical signs suggesting CAP (cough, fever, pleuritic chest pain or dyspnea) • New radiographic infiltrate • Severe CAP criteria: modified American Thoracic Society (ATS)[25], [See Appendix Table 3] or PSI class V • C-reactive protein >15mg/dL on admission
Exclusion	• Prior treatment with systemic corticosteroids (chronic or on admission) • Nosocomial pneumonia • Severe immunosuppression (HIV/immunosuppressive conditions/medications) • Major GI bleed within 3 months of hospitalization • Uncontrolled diabetes mellitus • Condition requiring acute treatment >1mg/kg/day of methylprednisolone or its equivalent • Pandemic H1N1 influenza
Outcomes	**Primary** **Early Treatment Failure:** • Clinical deterioration w/in 72 hrs[a] **Late Treatment Failure:** • Radiographic progression[b] • Persistence of respiratory failure[c] • Development of shock or need for invasive mechanical ventilation not present at baseline • Death between 72-120h after treatment initiation **Secondary** • Time to clinical stability • Length of ICU and hospital stay • In-hospital mortality
Intervention	**Interventions started within 36 hours of hospital admission** Methylprednisolone IV 0.5mg/kg every 12 hours x 5 days Placebo x 5 days
Statistics	• 60 patients needed in each group to detect a 20% reduction in treatment failure (assuming 35% treatment failure in the placebo group) • 80% power, 5% significance • Chi-square test or Fisher's exact test used to compare categorical variables • Continuous variables compared with Student´s t-test or the nonparametric Mann-Whitney U-test • Logistic regression models used to examine differences in primary outcome and in-hospital mortality, secondary outcomes assessed with Cox proportional hazard regression models • Interim analysis at 50% patient accrual (p<0.03, alpha 0.05 [Pocock Test]) • Intention to treat and per protocol analyses • Goodness of fit models were tested using the Hosmer-Lemeshow test

Baseline Characteristics

	Methylprednisolone (n=61)	Placebo (n=59)
Age, mean (SD),years	64.5 (19.1)	66.1 (20.1)
PSI Class I-III	18 (30%)	14 (24%)
PSI Class IV[+]	21 (34%)	26 (44%)
PSI Class V[+]	22 (36%)	19 (32%)

ICU Admission	43 (70%)	47 (80%)
Procalcitonin,ng/dL+	1.3 (0.4-4.4)	3.1 (0.8-9.5)
IL-10,pg/dL+	4.7 (2.8-9.2)	8.1 (4.0-13.5)
Septic Shock+	10 (17%)	18 (31%)
SBP <90 mmHg+	11 (18%)	17 (29%)
Pleural Effusion	11 (18%)	12 (20%)
Congestive Heart Failure	22 (36%)	24 (41%)
Macrolide Concentration	15 (24%)	13 (23%)
Mechanical Ventilation	5 (8%)	10 (17%)
Chronic Pulmonary Disease	7 (11%)	12 (20%)
Diabetes Mellitus	10 (16%)	13 (22%)
+ difference between groups= p value < 0.05		

Results

	Methylprednisolone (n=61)	**Placebo (n=59)**	**% Difference 95% CI**	**P Value**	**NNT**
Primary Outcomes					
Composite Treatment Failure (%)	8 (13)	18 (31)	18 (3-32)	0.2	---
Early Treatment Failure (0-72 hrs) (%)	6 (10)	6 (1)	0 (-10 to 11)	0.95	---
Late Treatment Failure (72-120 hrs) (%)	2 (3)	15 (25)	0.02-0.46	0.001	5
Radiographic Progression (%)	1 (2)	9 (15)	14 (4 to 23)	0.007	8
Late Septic Shock (%)	0	4 (7)	7 (0 to 13)	0.06	---
Secondary Outcomes					
In-Hospital Mortality (%)	6 (10)	9 (15)	5 (-6 to 17)	0.37	---
Time to Clinical Stability (IQR), days	4 (3 to 6)	5 (3 to 7)	1 (-0.4 to 2.4)	0.28	---
Safety Outcomes					
Hyperglycemia (%)	11 (18)	7 (12)	---	0.34	---

Author's Conclusions

Among patients with severe CAP and high initial inflammatory response, the acute use of methylprednisolone compared with placebo decreased treatment failure. If replicated, these findings would support the use of corticosteroids as adjunctive treatment in this clinical population.

Strengths

- Multi-center, double-blind, randomized, placebo-controlled
- Selected a homogenous population
- Antibiotic treatment was chosen based on the 2007 IDSA Guidelines; medications were reported
- Microbiological etiologies of pneumonia were reported
- Appropriate exclusion criteria

Weaknesses

- Outdated ATS criteria for severe pneumonia
- 49% of patients enrolled did not meet inclusion criteria; enrollment took 8 years; only represents a small population of CAP patients
- Composite outcome driven by radiographic progression; not normally a parameter measured in trials
- Larger studies are needed to show that less radiographic progression is linked to lower mortality rates
- Fluid given to patients was not clarified; specifically in septic shock patients
    - Could affect appropriate sepsis treatment and radiographs

	• Unbalanced baseline characteristics: more septic shock, IL-10, mechanically ventilated, levofloxacin monotherapy, and CHF patients in placebo group • Higher percentage of placebo shock patients received first dose of antibiotics after 4 hours (39% vs. 20%) • Low percentages of patients received macrolide antibiotics despite proven immunomodulatory effects (23% vs 24%) • Decision to switch IV→PO and discharge from ICU was left to the discretion of the medical team; no set rules • Short term follow up • No assessment of adrenal insufficiency at baseline • Did not find statistical power (predetermined treatment failure of 35%)
Take Away	• The inclusion criteria of C-reactive protein >15mg/dL is only representative of a small portion of CAP patients • Late treatment failure driven by radiographic progression; could be influenced by other parameters • No statistically significant difference in hyperglycemia events between the groups • Difficult to apply to practice due to possible influences on radiographic progression other than steroids
Footnotes	a. need for invasive mechanical ventilation and/or shock not present at baseline or death b. increase >50% of pulmonary infiltrates compared to baseline c. PaO_2/FiO_2 <200 with respiratory rate >30 min^{-1} in non-intubated patients

Table 6: 2015 Blum, et al.[26] Adjunct Prednisone Therapy for Patients with Community Acquired Pneumonia: A Multicentre, Double-Blind, Randomised, Placebo-Controlled Trial	
Objective	To assess whether short-term corticosteroid treatment reduces time to clinical stability in patients admitted to hospital for community-acquired pneumonia.
Design	Multi-center at 7 Swiss institutions, double-blind, randomized, placebo-controlled. Patients were assessed from December 2009 – May 2014.

Inclusion	• ≥ 18 years old
	• Hospital admission with CAP
	  ○ New infiltrate on chest radiograph + ≥ 1 of the following:
	  ▪ Signs and symptoms[a]
	  ▪ Core body temperature ≥38·0°C
	  ▪ Auscultatory findings of abnormal breathing sounds or rales
	  ▪ Leucocyte count > 10,000 cells/µL or < 4,000 cells/ µL

Exclusion	• Permanent inability for informed consent • Active IV drug use • Acute burn injury • GI bleeding in the past 3 months • Known adrenal insufficiency • Condition requiring >0.5 mg/kg/day of prednisone equivalent • Pregnancy or breastfeeding • Severe immunosuppression[b]

Outcomes

Primary	Secondary
▪ **Time to clinical stability** • Days until stable vital signs for ≥24 hrs ○ Temperature ≤37.8°C ○ Heart rate ≤ 100 bpm ○ Respiratory rate ≤24 ○ SBP ≥90 mmHg w/o vasopressors or ≥ 100 mmHg for patients with hypertension ○ Baseline mental status ○ Able to tolerate PO ○ PaO_2 ≥ 60 mmHg or pulse oximetry ≥ 90% Considered not stable if ≥1 criteria were not met	▪ Time to effective discharge ▪ Recurrence of pneumonia ▪ Re-admission to hospital ▪ ICU admission ▪ All-cause mortality ▪ Duration of total and IV antibiotic treatment ▪ Disease activity score specific to CAP (CAP SCORE) [See Appendix Figure 1][27] ▪ Complications of CAP[c] ▪ Side effects of corticosteroids[d] ▪ Time to earliest possible hospital discharge ▪ ICU patients • Length of ICU stay • Time to transfer to ICU • Time to discharge from ICU • Duration of vasopressors • Duration of mechanical ventilation

Intervention

Prednisone 50mg PO daily x 7 days	Placebo x 7 days

Statistics

Sample size of 800 patients needed for a power of 85% for estimated decrease in the risk of non-stability after 1 week in survivors by 25% with the use of steroids; intention to treat; Cox proportional hazards regression used to calculate an unadjusted hazard ratio, 95% confidence interval

Baseline Characteristics

	Prednisone (n=392)	Placebo (n=393)
Age (years)	74 (61-83)	73 (61-82)
PSI Class I	47 (12%)	45 (11%)
PSI Class II	72 (18%)	69 (18%)
PSI Class III	71 (18%)	95 (24%)
PSI Class IV	148 (38%)	132 (34%)
PSI Class V	54 (14%)	52 (13%)
CAP SCORE, points	43 (30-60)	46 (29-63)
C-reactive protein (mg/dL)	15.9 (8.03-24.5)	16.4 (7.91-25.0)
COPD	73 (19%)	60 (15%)
Diabetes mellitus	77 (20%)	78 (20%)
Temperature (°C)	37.6 (37-38.2)	37.6 (37-38.2)
Systolic Blood Pressure (mmHg)	124 (119-140)	123 (110-140)
Heart Rate (beats/min)	84 (74-95)	82 (72-96)
Respiratory Rate (breaths/min)	20 (18-24)	20 (18-24)
SaO_2 (%)	95 (92-96)	94 (92-97)
Confusion	22 (6%)	29 (7%)

Results

	Prednisone (n=392)	Placebo (n=393)	HR or OR (95% CI)	P value	NNH
Time to Clinical Stability (days)	3.0 (2.5-3.4)	4.4 (4.0-5.0)	HR 1.33(1.15-1.50)	<0.0001	
Time to Effective Discharge (days)	6.0 (6.0-7.0)	7.0 (7.0-8.0)	HR 1.19(1.04-1.38)	0.012	

	Recurrent Pneumonia	23 (6%)	18 (5%)	OR 1.30 (0.69-2.44)	0.42	
	Death from Any Cause	16 (4%)	13 (3%)	OR 1.24 (0.59-2.62)	0.57	
	ICU Admission	16 (4%)	22 (6%)	OR 0.72 (0.37-1.39)	0.42	
	IV Antibiotic Treatment (days)	4.0 (3.0-6.0)	5.0 (3.0-7.0)	Difference –0·89 days (–1·57 to –0·20) days	0.011	
	Hyperglycemia Requiring Insulin	76 (19%)	43 (11%)	OR 1.97 (1.31-2.93)	0.0010	13
Author's Conclusions	Prednisone treatment for 7 days in patients with community-acquired pneumonia admitted to hospital shortens time to clinical stability without an increase in complications. This finding is relevant from a patient perspective and an important determinant of hospital costs and efficiency.					
Strengths	• Intention to treat • Randomized, placebo-controlled, double-blind, multi-center • Large sample size • Procalcitonin was used to guide treatment duration • Funding source had no role in the study • Baseline characteristics balanced between groups • Used a PO dosage form • Longer term follow-up in comparison to the majority of other studies • Excluded patients with adrenal insufficiency • Listed the microbiological etiologies of pneumonia • Majority of patients received a macrolide					
Weaknesses	• Not powered for mortality • Subjective primary outcome • Composite end-point; steroids can favorably affect systolic blood pressure (SBP) and fever • Heterogeneous population • Despite ~50% of patients following into PSI IV/V, clinical signs were near normal • Fever reduction affects IV → PO conversion • Insulin treatment may have led to un-blinding • Did not exclude influenza patients					
Take Away	• According to the findings, steroids decreased time to clinical stability by ~1.5 days and time to discharge by 1 day • Primary outcome is subjective and could have been influenced by steroids' ability to affect fever and SBP • Steroids led to insulin-required hyperglycemia in 19% vs. 11% of patients (p=0.0010) • Population in study was not severely ill; cannot apply findings to severely ill patients					
Footnotes	a. cough, sputum production, dyspnea b. HIV and a CD4 cell count < 350 cells/µL, immunosuppressive therapy after solid organ transplantation, neutropenia < 500 cells/µL or neutrophils of 500–1000 cells/µL during ongoing chemotherapy with an expected decrease to values < 500 cells/µL, cystic fibrosis, or active tuberculosis c. acute respiratory distress syndrome, empyema, persistence of pneumonia d. hyperglycemia, hypertension, delirium, nosocomial infections, weight gain					

Meta-Analysis and Systematic Review:

Table 7: 2015 Siemieniuk, et al.[28]
Corticosteroid Therapy for Patients Hospitalized With Community-Acquired Pneumonia: A Systematic Review and Meta-Analysis

Objective	To examine the effect of adjunctive corticosteroid therapy on mortality, morbidity, and duration of hospitalization in patients with CAP.
Design	Systematic review and meta-analysis of 13 studies

Inclusion	• CAP studies randomized to oral or IV corticosteroid therapy vs. placebo or no treatment
	  ○ Reported on at least 1 of the following outcomes:
	  ▪ Duration of hospitalization
	  ▪ Time to clinical stability
	  ▪ All-cause mortality
	  ▪ Need for mechanical ventilation
	  ▪ Need for ICU admission
	  ▪ Development of ARDS

Exclusion	• Studies of ventilator associated pneumonia, aspiration pneumonia, *Pneumocystis jirovecii*, or those limited to patients with chronic obstructive pulmonary disease
Outcomes	• All-cause mortality • Mechanical ventilation • ICU admission • ARDS • Duration of hospitalization • Time to clinical stability • Adverse effects

Population

Study	Patients,n	Mean Age	Follow-Up (days)	Inclusion	Intervention
Blum, 2015	784	74	30	Age≥18, ATS criteria for CAP	Prednisone 50mg PO daily x 7 days
Confalonieri, 2005	46	63.5	60	CAP w/ 1993 ATS severe criteria	Hydrocortisone 200mg IV bolus; 10mg/hr x 10 days
El-Ghamawy, 2006	34	61.8	In-hospital	Age≥18, ATS criteria for severe CAP requiring ICU admission	Hydrocortisone 200mg IV bolus; 10mg/hr x 7 days
Fernandez-Serrano, 2011	45	63.5	1 month	Age≥18 and ≤75, severe CAP w/ consolidation of ≥2 lobes and PO_2/FiO_2<300	Methylprednisolone 200mg IV bolus; tapering infusion (3.3 to 0.8 IV/h) over 9 days
Marik, 1993	30	36.2	ICU discharge	Age≥18 and ≤70, BTS criteria for severe	Hydrocortisone 10mg/kg IV 30 min before antibiotics
McHardy, 1972	126	60.3	In-hospital	Age ≥12, clinical diagnosis of pneumonia	Prednisolone 5 mg Q 6 hrs PO x 7 days
Meijvis, 2011	304	63.9	30	Age≥18, CAP by PSI criteria	Dexamethasone 5 mg IV daily x 4 days
Mikami, 2007	31	72	In-hospital	Any CAP, non-severe	Prednisolone 40 mg

				by ATS	IV x 3 days
Nafae, 2013	80	49	In-hospital	Age≥18, CAP by PSI criteria	Hydrocortisone 200mg IV bolus; 10mg/hr x 7 days
Sabry, 2011	80	62.2	8 days	Adults with severe CAP by ATS	Hydrocortisone 200mg IV bolus; 12.5mg/hr x 7 days
Snijders, 2010	213	63.5	30 days	Age≥18 hospitalized with CAP	Prednisolone 40 mg IV/PO x 7 days
Torres, 2015	120	65.3	In-hospital	Age ≥18 with severe CAP by ATS or PSI criteira and CRP >150mg/L	Methylprednisolone 0.5mg/kg IV BID x 5 days
Wagner, 1956	113	52% <40	In-hospital	Culture confirmed pneumococcal pneumonia	Hydrocortisone PO Q 6 hrs; 80-100mg tapering over 5 days

Methods

- MEDLINE, EMBASE, the Cochrane Central Register of Controlled Trials, searched until May 24, 2015
- GRADE system to assess the certainty of evidence
- Publication bias was assessed through the funnel plot method
- A modified Cochrane instrument was used to assess risk of bias of primary studies
- Used an α of 0.05 and a β of 0.08 to measure optimal size calculations
- Mantel-Haenszel risk ratios for dichotomous outcomes and mean differences for continuous variables
- I^2 was used to test for heterogeneity
- Hartung-Knapp-Sidick-Jonkman method used to calculate 95% CIs

Results

Outcome	RR 95% CI	Risk Difference	Certainty
Mortality n=1974;12 studies	0.67 (0.45 – 1.01)	2.8%	Moderate
Need for Mechanical Ventilation n=1060;5 studies	0.45 (0.26 – 0.79)	5.0%	Moderate
ICU Admission N=950;3 studies	0.69 (0.46 – 1.03)	4.2%	Moderate
ARDS N=945;4 studies	0.24 (0.10 – 0.56)	6.2%	Moderate
Hyperglycemia N=1534;6 studies	1.49 (1.01 – 2.19)	3.5%	High
Outcome	**Mean Difference 95% CI**		**Certainty**
Time to Clinical Stability N=1180;5 studies	-1.22 ([-2.08] – [-0.35])		High
Duration of Hospitalization N=1499;6 studies	-1.00 ([-1.79] – [-0.21])		High

Author's Conclusions

For hospitalized adults with CAP, systemic corticosteroid therapy may reduce mortality by approximately 3%, need for mechanical ventilation by approximately 5%, ARDS by approximately 6%, and hospital stay by approximately 1 day.

Strengths

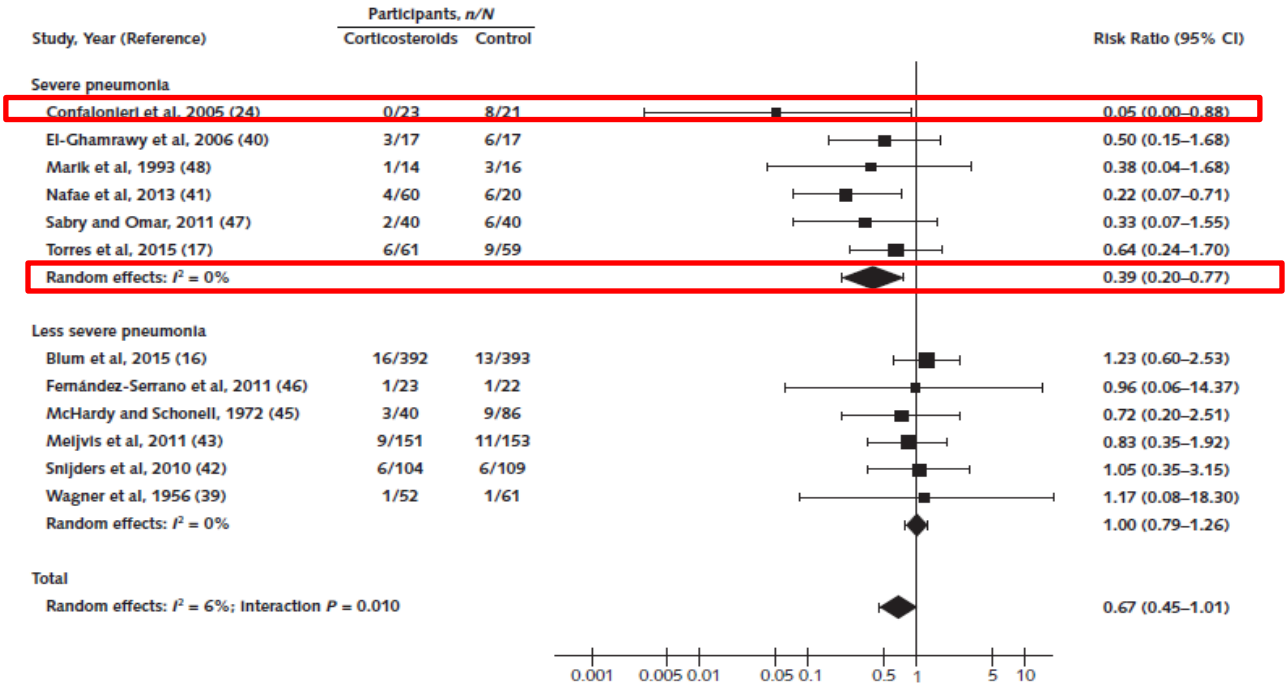
- Only included randomized controlled trials
- Appropriately defined severe pneumonia
- Included studies from various countries
- Assessed for bias using the GRADE system
- Performed subgroup and sensitivity analyses

	• Specific and appropriate eligibility requirements
Weaknesses	• Heterogeneous severity of illnesses, steroid medications, doses, routes of administrations, durations of treatments • Trials excluded patients at highest risk of adverse events • Mortality outcome patient number was less than calculated optimal information size (n=3500) to detect relative reduction of 35% • Difficult to draw conclusions for duration of hospitalization due to high degree of heterogeneity
Take Away	• Analyzed appropriate randomized controlled trials • ARDS and need for mechanical ventilation results are reported based on a small number of events in a limited number of studies; serious limitation • Clinical stability and duration of hospitalization are the only outcomes with high certainty; moderate/high heterogeneity, respectively

Mortality and Severity of Illness

A. Mortality Benefits Based on Severity of Illness:

Figure 3: All-Cause Mortality By Severity of Illness[28]



a) Subgroup Analysis from Simumek et al.[28]

i. The number of patients included in the mortality outcome was smaller than the calculated optimal information size (n=3500) to detect relative reduction of 35%.

ii. The outcome of mortality was primarily driven by Confalonieri et al.

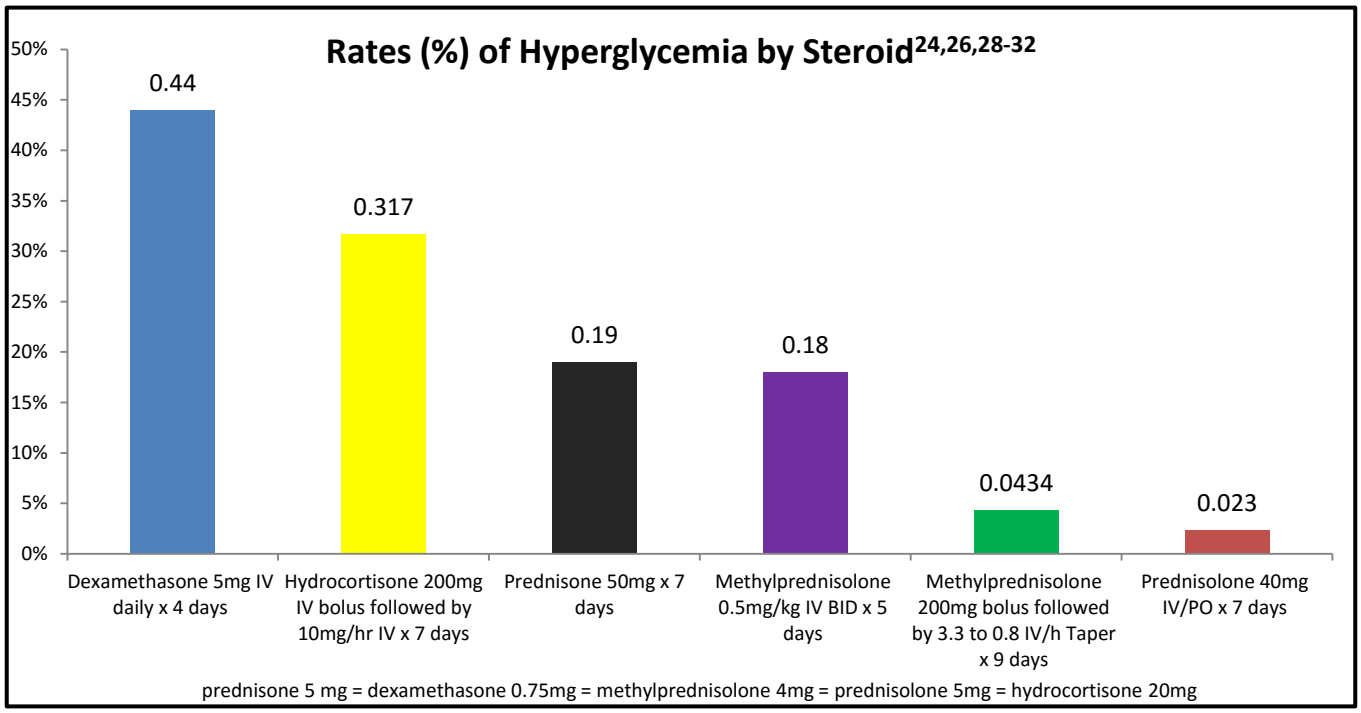
1. Baseline characteristics were unbalanced.
   - Lower C-reactive protein and PaO_2/FiO_2 in placebo group
2. Small sample size.
3. High risk of publication bias.
4. Study stopped early.

b) Mortality Based on Severity of Illness:

i. Corticosteroids are more likely to have a mortality benefit in severe CAP patients but this is not with high certainty.

Assessing Hyperglycemia Risks:

Figure 4: Hyperglycemia Rates Based on Steroids



A. Hyperglycemic Risk

a) Siemieniuk et al found in their meta-analysis that corticosteroids increased the risk of hyperglycemia requiring insulin.[28]

b) Hyperglycemia is an adverse effect with corticosteroid use and can be appropriately treated with insulin.

c) Retrospective studies have demonstrated that hyperglycemia increases the risk of mortality; however, no long term adverse effects from hyperglycemia were observed in the presented studies and meta-analysis[28,33,34]

Ongoing Studies Evaluating Steroids in CAP:

Table 8: Ongoing Studies in CAP

Study	Design	Primary Outcome	Population	Intervention	Follow-Up
ADRENAL[35]	Randomized, Placebo Controlled, Double-blind, Multi-Center	All-cause mortality at 90 days	N=3800 ICU patients with septic shock	Hydrocortisone 200mg IV continuous infusion/24 hours vs. placebo x 7 days	90 days
ESCAPe[36]	Randomized, Double-blind, Multi-Center	All-cause mortality at 60 days	N=1450 hospitalized patients with severe CAP based on ATS criteria	Methylprednisolone IV bolus; 40mg/day x 7 days; 20mg/day x 7 days; 12mg/day x 3 days; 4mg/day x 3 days vs. placebo	180 days

Summary and Conclusions:

A. Use of corticosteroids in CAP has been associated with decreased time to clinical stability and duration of hospitalization; however, these outcomes are subjective and left to the discretion of the physician. Time to clinical stability may be influenced by steroids effect on vital signs such as blood pressure and temperature.

B. Steroids cannot currently be suggested for mortality benefit in CAP patients. Current literature suggests a higher benefit for severe CAP patients; however, this result is driven by weak evidence.

C. The main adverse effect observed in randomized controlled trials was hyperglycemia. According to the meta-analysis, corticosteroids increase the incidence of insulin-required hyperglycemia and no long-term effects were observed. Current literature is limited by short-term follow-up.

D. If a clinician chooses to use corticosteroids for CAP patients, there is no consensus on which medication, dose, route, or frequency is preferred. Also, patients that are immunosuppressed, pregnant, at high risk for neuropsychiatric events, and had a recent gastrointestinal hemorrhage were commonly excluded in trials; therefore, use in this population has not been studied.

E. The idea of corticosteroids should not be "suppressed." The benefits of corticosteroids are still debatable due to small sample sizes of trials, risks of bias, and short term follow-up. The results of large, well-designed, randomized-controlled trials with long term follow-up such as ESCAPe and ADRENAL are needed to confirm benefits and rule out long term risks of corticosteroids.

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Appendix

Table 1: Pneumonia Definitions[3]		
Hospital-Acquired Pneumonia (HAP)	**Health-Care Associated Pneumonia (HCAP)**	**Ventilator-Associated Pneumonia (VAP)**
Occurs ≥ 48 hour of hospital admission	Hospitalization ≥ 2 days within 90 days of infection	Occurs ≥ 48 hour after endotracheal intubation
	Resided in nursing home or long-term care facility	
	IV antibiotic therapy in the past 30 days of current infection	
	Chemotherapy in the past 30 days of current infection	
	Wound care within the past 30 days of current infection	
	Attended a hospital or hemodialysis clinic	

Table 2: Pneumonia Severity Index (PSI)[21]			
Risk Factor	**Points**	**Risk Class**	**Mortality Risk**
Men	Age		
Women	Age Minus 10		
Nursing Home Resident	+10		
Neoplasm	+30		
Liver Disease	+20		
Heart Failure	+10		
Stroke	+10		
Renal Failure	+10		
Altered Mental Status	+20		
Respiratory Rate ≥30	+20		
Systolic Blood Pressure <90 mmHg	+20		
Temperature < 95°F or ≥104°F	+15		
Pulse ≥125 bpm	+10		
Arterial pH <7.35	+30		
BUN >30 mg/dL	+20		
Sodium < 130 mmol/L	+20		
Glucose > 250 mg/dL	+10		
Hematocrit <30%	+10		
Partial Pressure of arterial O_2 < 60 mmHg	+10		
Pleural Effusion	+10		
	<51	I	0.1 – 0.4%
	51-70	II	0.6 – 0.7%
	71-90	III	0.9 –2.8%
	91-30	IV	8.5 – 9.3%
	>130	V	27 – 31.1%

Table 3: 2007 ATS Criteria for Severe CAP[25]	
Major Criteria	**Minor Criteria**
• Invasive mechanical ventilation • Septic shock with the need for vasopressors	• Respiratory rate ≥30 breaths/min • PaO_2/FiO_2 ratio ≤250 • Multi-lobar infiltrates • Confusion/disorientation • Uremia (BUN ≥20 mg/dL) • Leukopenia (WBC <4,000 cells/mm^3) • Thrombocytopenia (platelets <100,000 cells/mm^3) • Hypothermia (core temperature <36°C) • Hypotension requiring aggressive fluid resuscitation
ICU admission or high-level monitoring unit is recommended when 3 of the minor or 1 of the major criteria are present	

Proposed Modified ATS Rule for Severe CAP[24]	
Major Criteria	**Minor Criteria**
• Requirement for mechanical ventilation • Septic shock	• PaO_2/FiO_2 <250 • Multi-lobar involvement • Systolic blood pressure <90 mmHg
ICU admission recommended if 2 out of the 3 minor criteria or 1 major criteria are met	

Table 4:CURB-65[10]				
Acronym	**Factors**	**Score**	**30 Day Mortality Risk:**	**Admission:**
C	Confusion	1		
U	BUN (>20mg/dL)	1		
R	Respiratory Rate (≥30 breaths/min)	1		
B	Blood Pressure (Systolic < 90 mmHg/diastolic ≤60 mmHg)	1		
65	Age ≥ 65	1		
		0	0.7%	Outpatient
		1	2.1%	Outpatient
		2	9.2%	Ward
		3	14.5%	ICU
		4	40%	ICU
		5	57%	ICU

Table 5: Corticosteroid Equivalencies[37]					
	Potency Relative to Hydrocortisone			Half-Life	
	Equivalent Glucocorticoid Dose (mg)	Anti-inflammatory	Mineral-Corticoid	Plasma (minutes)	Duration of Action (hours)
Short Acting					
Hydrocortisone (Cortef, Cortisol)	20	1	1	90	8-12
Cortisone Acetate	25	0.8	0.8	30	8-12
Intermediate Acting					
Prednisone	5	4	0.8	60	12-36
Prednisolone	5	4	0.8	200	12-36
Triamcinolone	4	5	0	300	12-36
Methylprednisolone	4	5	0.5	180	12-36
Long Acting					
Dexamethasone	0.75	30	0	200	36-54
Betamethasone	0.6	30	0	300	36-54
Mineralocorticoid					
Fludrocortisone	0	15	150	240	24-36
Aldosterone	0	0	400+	20	----

Figure 1: CAP Questionnaire:[26]

Question	level	coding
1. Are you today (XXth day of the evaluation) bothered by shortness of breath when		
	sitting still	¤ yes ¤ no
	walking around the house/ward	¤ yes ¤ no
	washing/dressing	¤ yes ¤ no
	walking in the street	¤ yes ¤ no
	taking a shower	¤ yes ¤ no
	walking the stairs	¤ yes ¤ no
2. If you were to give a mark on a 1 to 5 scale expressing the severity of your shortness of breath at the moment, which mark would that be?		
	not at all short of breath (1)	¤
	slightly short of breath (2)	¤
	fairly short of breath (3)	¤
	substantially short of breath (4)	¤
	terribly short of breath (5)	¤
3a. Do you cough?		
	no (skip questions 3b, c and d)	¤
	only in the morning, when getting up	¤
	now and then, all through the day	¤
	frequently, all through the day	¤
3b. Do you cough up sputum? (amount of sputum by 24 hrs)		
	no	¤
	less than 2 spoons	¤
	more than 2 spoons	¤
	half a cup or more	¤
3c. Do you cough up the sputum with ease?		
	not bothered by sputum	¤
	with ease	¤
	fairly difficult	¤
	very difficult	¤
3d. What is the color of the sputum?		
	did not pay attention/no sputum	¤
	transparent	¤
	white	¤
	green, yellow or brown	¤
4. When the following statement is correct, please check the leftmost box, the less you agree with the statement, one of the boxes on the right can be ticked off		
I feel fit	yes, that is correct	¤ ¤ ¤ ¤ ¤ no, that is not correct
5. If you were to give a mark on a 1 to 5 scale expressing your general state of health at the moment, which mark would that be?		
	excellent (1)	¤
	good (2)	¤
	fair (3)	¤
	poor (4)	¤
	very poor (5)	¤

Figure 2: CAP Questionnaire:[26]

Item*		Quantification	CAP	Respiratory	Well being
Shortness of breath					
walking the stairs	☐ yes 1				
taking a shower	☐ yes 1				
walking in the street	☐ yes 1				
washing/dressing	☐ yes 1				
walking around the	☐ yes 1				
house/ward	☐ yes 1				
sitting still					
	0	☐ 6			
subtotal (sum)	1	☐ -2			
	2-3	☐ -6	→ _____	→ _____	
	4-6	☐ -8			
Severity of shortness of breath					
not at all short of breath (1)		☐ 7			
slightly short of breath (2)		☐ -2			
fairly short of breath (3)		☐ -8	→ _____	→ _____	
substantially short of breath (4)		☐ -11			
terribly short of breath (5)		☐ -13			
Cough					
No		☐ 9			
only in the morning, when getting up		☐ -6			
now and then, all through the day		☐ -6	→ _____	→ _____	
frequently, all through the day		☐ -12			
Cough up sputum					
None		☐ 7			
less than 2 spoons		☐ -8			
more than 2 spoons		☐ -13	→ _____	→ _____	
half a cup or more		☐ -16			
Cough up sputum with ease					
no sputum		☐ 7			
with ease		☐ -9			
fairly difficult		☐ -10	→ _____	→ _____	
very difficult		☐ -10			
Colour of sputum					
did not pay attention/no sputum		☐ 8			
transparent		☐ -8			
white		☐ -8	→ _____	→ _____	
green, yellow or brown		☐ -14			
Feeling fit					
yes, that is correct		☐ 12			
		☐ 4			
		☐ 0	→ _____		→ _____
		☐ -6			
no, that is not correct		☐ -11			
General state of health					
excellent (1)		☐ 14			
good (2)		☐ 8			
moderate (3)		☐ -1	→ _____		→ _____
poor (4)		☐ -9			
very poor (5)		☐ -15			
Raw total		*(sum)*	_____ (A)	_____ (B)	_____ (C)

SCALE TRANSFORMATION

CAP SCORE	**= (A + 99) / 1.69**	_____
RESPIRATORY SCORE	**= (B + 73) / 1.17**	_____
WELL BEING CORE	**= (C + 26) / 0.52**	_____