Adjunctive Treatment of Community-Acquired Pneumonia: A New Role of Corticosteroids?

Sarah Klembith, Pharm.D.
PGY1 Pharmacy Resident
Central Texas Veterans Health Care System
The University of Texas at Austin College of Pharmacy
January 15, 2016

Learning Objectives:
1. Understand the epidemiology, pathophysiology, diagnosis, and severity of pneumonia
2. Review current guidelines for the treatment of community-acquired pneumonia
3. Review corticosteroids and their role in inflammation
4. Analyze literature regarding the benefit of corticosteroids in the treatment of community-acquired pneumonia
5. Formulate recommendations regarding the use of corticosteroids in community-acquired pneumonia
BACKGROUND: PNEUMONIA

I. Epidemiology
   A. Over five million adults are affected by community-acquired pneumonia (CAP) each year in the United States (U.S.)\(^1\)
   B. High morbidity and mortality
      1. Pneumonia and influenza combined\(^2\)
         a. Eighth leading cause of death in the U.S.
         b. Most common cause of infection-related mortality
      2. Despite advances in antimicrobial therapy, rates of mortality due to pneumonia have not decreased significantly\(^2\)
         a. Hospital inpatient deaths: 3.4%
         b. Mortality rate for CAP patients admitted to intensive care unit (ICU) ranges from 21-58\(^{\%}\)\(^1\)
   C. Pneumonia occurs at all ages\(^3\)
      1. More common in elderly
   D. Estimated annual economic burden of CAP in the U.S. exceeds 10 billion dollars\(^4\)

II. Pneumonia classification\(^3\)
   A. Community-acquired: no contact to a medical facility
   B. Hospital-acquired: developing >48 hours after hospital admission
   C. Healthcare-associated: non-hospitalized patients at risk of multi-drug resistant (MDR) pathogens
      1. Two or more risk factors for MDR pathogen
         a. Recent hospitalization ≥2 days within past 90 days
         b. Nursing home or long-term care facility resident
         c. Recent antibiotic use (past 30 days), chemotherapy, wound care, or infusion therapy
         d. Hemodialysis
         e. Contact with family member with infection caused by MDR pathogen
   D. Ventilator-associated: developing >48 hours after intubation and mechanical ventilation

III. Pathophysiology\(^3\)
   A. Pathogen enters lower respiratory tract by three routes
      1. Inhaled
      2. Hematogenous
      3. Aspiration (oropharyngeal contents)
   B. Components of innate immune system fail to clear pathogen
      1. Normally expelled by mucociliary clearance, cough, antimicrobial peptides, and local innate immune defenses\(^5\)
   C. Systemic inflammation follows\(^6-8\)
      1. Increased pro-inflammatory cytokines
      2. High levels of inflammation are associated with higher rates of treatment failure
      3. Patients with severe CAP are found to have relative adrenal insufficiency
   D. Can progress to acute respiratory failure, septic shock, multi-organ failure, and death if left untreated
   E. Most common pathogens in CAP\(^3,9\)
      1. *Streptococcus pneumoniae* - most common
      2. Atypical organisms: *Mycoplasma pneumoniae, Legionella* species, *Chlamydophila pneumoniae*
      3. *Haemophilus influenzae*
      4. Variety of viruses
   F. Risk factors\(^3\)
      1. Chronic obstructive pulmonary disease (COPD)
      2. Human immunodeficiency virus (HIV) infection
      3. Diabetes mellitus
      4. Age >65 years
      5. Depressed mucociliary transport
         a. Ethanol and narcotic use
         b. Bronchus obstruction
      6. Altered sensorium and neuromuscular disease – may result in increased inoculum size

IV. Clinical presentation
   A. Signs and symptoms\(^3,5,10\)
      1. Begins as mild upper-airway irritation
      2. Fever, chills, malaise, cough, dyspnea, pleuritic chest pain
      3. Rust-colored sputum or hemoptyis
B. Physical exam
1. Tachypnea and tachycardia
2. Dullness to percussion
3. Diminished breath sounds over affected area
4. Inspiratory crackles
5. Increased tactile fremitus, whispered pectoriloquy, and egophony
6. Chest wall retractions
C. Often more subtle in older patients
1. Often presents with weakness and decline in functional or mental status

V. Diagnosis
A. Lung imaging showing infiltrate required for diagnosis
1. Chest radiograph most common
   a. Dense lobar or segmental infiltrate
   b. Patchy consolidation occasionally
   c. Lobar consolidation, cavitation, and pleural effusions suggest a bacterial etiology
B. Clinical features
1. Cough
2. Fever
3. Pleuritic chest pain
C. Laboratory testing
1. Investigated for specific pathogens that would significantly alter standard empirical management
   a. Overall low yield and infrequent positive impact on clinical care
      i. Against routine use of common tests (blood and sputum cultures)
   b. Specific clinical indications for more extensive diagnostic testing (Appendix A)
      i. Result will likely change individual antibiotic management
2. Sputum and blood cultures recommended for inpatients with severe illness

VI. Severity and site-of-care decision
A. Hospitalization recommended
1. CURB-65 score ≥2 (moderate recommendation)
   a. Confusion
   b. Blood urea nitrogen (BUN) ≥20 mg/dL
   c. Respiratory rate ≥30 breaths/min
   d. Systolic blood pressure <90 mm Hg or diastolic blood pressure ≤60 mm Hg
   e. Age ≥65 years
2. Pneumonia Severity Index (PSI) risk class IV and V
   a. Assesses patient demographics, comorbidities, physical examination findings, laboratory and radiographic findings
   b. Risk stratification into five severity classes
3. Objective criteria of scores should always be supplemented with clinical judgement
B. Direct admission to ICU
1. One major criteria for severe pneumonia (strong recommendation)
   a. Septic shock requiring vasopressors
   b. Acute respiratory failure requiring intubation and mechanical ventilation
2. Three or more minor criteria for severe pneumonia (moderate recommendation)
   a. Respiratory rate ≥30 breaths/minute
   b. Arterial oxygen pressure/fraction of inspired oxygen (PaO₂/FiO₂) ratio ≤250
   c. Multilobar infiltrates
   d. Confusion/disorientation
   e. BUN level ≥20 mg/dL
   f. Leukopenia resulting from infection (white blood cell [WBC] count <4000 cells/mm³)
   g. Thrombocytopenia (platelet count <100,000 cells/mm³)
   h. Hypothermia (core temperature <36°C)
   i. Hypotension requiring aggressive fluid resuscitation
TREATMENT GUIDELINES: COMMUNITY-ACQUIRED PNEUMONIA

I. Infectious Diseases Society of America/American Thoracic Society (IDSA/ATS) CAP Guidelines
   A. Empirical antimicrobial therapy depending on site-of-care decision, risk factors for drug-resistant pathogens, and comorbidities (Appendix C)
      1. First dose of antibiotic should be given while still in the emergency department (ED) if admitted through the ED
   B. Duration of antibiotics (moderate recommendation)
      1. Treated for a minimum of 5 days
      2. Afebrile for 48-72 hours
      3. No more than one CAP-associated sign of clinical instability before discontinuation of therapy
   C. Criteria for clinical stability
      1. Temperature ≤37.8°C
      2. Heart rate ≤100 beats/min
      3. Respiratory rate ≤24 breaths/min
      4. Systolic blood pressure ≥90 mm Hg
      5. Arterial oxygen saturation ≥90% or partial pressure of oxygen (pO2) ≥60 mm Hg on room air
      6. Ability to maintain oral intake
      7. Normal mental status

II. Adjunctive corticosteroid recommendations

Table 1. Corticosteroid recommendations according to various pneumonia guidelines

<table>
<thead>
<tr>
<th>Guideline</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>BTS, 2015 annotated</td>
<td>• Steroids are not recommended in the routine treatment of high severity CAP</td>
</tr>
</tbody>
</table>
| NICE, 2014               | • Do not routinely offer glucocorticosteroids in CAP unless patient has other conditions for which treatment is indicated  
                            • Benefit of glucocorticoid treatment seen in ICU setting; however, cannot make specific positive recommendation in this setting |
| Dutch, 2011              | • Corticosteroids are not recommended as adjunctive therapy                   |
| IDSA/ATS, 2007           | • Screen patients with severe CAP for corticosteroid insufficiency and replacement is appropriate if inadequate cortisol levels are documented  
                            • Criteria for steroid replacement remains controversial  
                            • Recommend tight glucose control if corticosteroids administered |

GLUCOCORTICOIDS AND INFLAMMATION

I. Inflammation
   A. Reflexive response to detection of microbial infection
   B. Complement and toll-like receptors activated
   C. Synthesis and release of inflammatory mediators
   D. Effects on the vasculature
      1. Localized vasodilation
      2. Increased vascular permeability
      3. Extravasation of plasma proteins
      4. Migration of leukocytes
   E. Beneficial role in inhibition and elimination of primary infection
   F. Excessive or persistent inflammation leads to tissue destruction and disease
      1. Down-regulation of inflammatory response may improve clinical course of CAP
         a. Glucocorticoids are one of the most prescribed classes of anti-inflammatory medications worldwide

II. Endogenous glucocorticoids
   A. Hypothalamic-pituitary-adrenal axis
      1. Hypothalamus secretes corticotropin-releasing hormone (CRH)
      2. CRH stimulates release of corticotropin from anterior pituitary
      3. Corticotropin induces synthesis and secretion of cortisol by adrenal cortex
B. Glucocorticoid receptor
1. Expressed in virtually all cells
2. Steroid hormone receptor family
3. High affinity for cortisol
4. Pleiotropic effects of glucocorticoid receptors on multiple signaling pathways

C. Cortisol anti-inflammatory actions by inhibiting synthesis of cytokines and inflammatory mediators by several pathways (Appendix D)
1. Cortisol-glucocorticoid receptor complex binds glucocorticoid-responsive elements in the nucleus and facilitates or inhibits transcription
   a. Induction and activation of annexin I
      i. Annexin I inhibits cytosolic phospholipase A₂α (cPLA₂α) and blocks release of arachidonic acid and subsequent conversion to eicosanoids (prostaglandins, thromboxanes, prostacyclins, and leukotrienes)
   b. Induction of mitogen-activated protein kinase (MAPK) phosphatase 1
      i. Inactivates Jun N-terminal kinase and prevents kinase cascade
         (i) Inhibits transcription of inflammatory and immune genes
      ii. May inhibit cPLA₂α by blocking its phosphorylation by MAPKs
   c. Cortisol-glucocorticoid receptor complex directly interferes with c-Jun-mediated transcription through protein-protein interactions
2. Interaction between cortisol-glucocorticoid receptor complex and other transcription factors regulate other glucocorticoid-responsive genes
   a. Inhibit nuclear factor-κB (NF-κB) transcription activity
      i. Blocks production of cytokines, chemokines, cell-adhesion molecules, complement factors
      ii. Repression of NF-κB-induced transcription of cyclooxygenase-2 (COX-2)
   b. Occurs at lower cortisol levels
3. Glucocorticoid signaling through membrane-associated receptors and second messengers

III. Exogenous glucocorticoids
A. Comparison of available glucocorticoids

Table 2. Glucocorticoid relative potencies and doses

<table>
<thead>
<tr>
<th>Glucocorticoid</th>
<th>Equivalent Dose* (mg)</th>
<th>Relative Anti-Inflammatory Activity</th>
<th>Relative Mineralocorticoid (sodium-retaining) Activity</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Short-acting</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hydrocortisone (cortisol)</td>
<td>20</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Cortisone acetate</td>
<td>25</td>
<td>0.8</td>
<td>0.8</td>
</tr>
<tr>
<td><strong>Intermediate-acting</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prednisone</td>
<td>5</td>
<td>4</td>
<td>0.8</td>
</tr>
<tr>
<td>Prednisolone</td>
<td>5</td>
<td>4</td>
<td>0.8</td>
</tr>
<tr>
<td>Methylprednisolone</td>
<td>4</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>Triamcinolone</td>
<td>4</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td><strong>Long-acting</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dexamethasone</td>
<td>0.75</td>
<td>30</td>
<td>0</td>
</tr>
<tr>
<td>Betamethasone</td>
<td>0.75</td>
<td>25</td>
<td>0</td>
</tr>
</tbody>
</table>

* Oral or intravenous (IV) administration

B. Numerous indications
C. Mechanism of action
1. Same as endogenous cortisol
D. Glucocorticoid dosing and pharmacokinetics (Appendix E)
E. Discontinuation
1. Gradual withdrawal by tapering dose to prevent adrenal suppression
   a. Long-term therapy
   b. High doses (>20 mg/day of prednisone or equivalent for >3 weeks)
F. Drug-drug interactions
1. Immunosuppressants
2. Non-steroidal anti-inflammatory drugs (NSAIDs)
3. Warfarin
4. Fluoroquinolones  
5. Live and inactivated vaccines  
6. Salicylates  
7. Antidiabetic agents  
8. Antacids  

G. Adverse effects from high-dose or prolonged glucocorticoid therapy\(^{15,19}\)  
1. Hyperglycemia  
2. Osteoporosis  
3. Hypertension  
4. Immunosuppression (increased incidence of secondary infection, mask acute infection, prolong or exacerbate viral infections, limit response to inactivated vaccines)  
5. Psychiatric disturbances (severe depression, euphoria, insomnia, mood swings, personality changes, psychosis)  
6. Growth retardation in children  
7. Inhibition of wound repair  
8. Myopathy  
9. Increased intraocular pressure, open-angle glaucoma, and cataracts  
10. Peptic ulcer (with possible perforation and hemorrhage)  

IV. Clinical Question  
A. Does treatment with adjunctive corticosteroids improve clinical outcomes in patients with CAP?
### Table 3. Summary of early trials of adjunctive corticosteroid therapy in CAP

<table>
<thead>
<tr>
<th>Study, Year (Location)</th>
<th>Study Design</th>
<th>N</th>
<th>Sample</th>
<th>Primary Outcome</th>
<th>Corticosteroid Agent and Duration</th>
<th>Results</th>
</tr>
</thead>
</table>
| Confalonieri, 2005<sup>21</sup> (Italy) | Randomized, double-blind, placebo-controlled, multicenter | 46   | Severe CAP in ICU treatment | PaO₂:FiO₂ | Hydrocortisone 200 mg IV bolus, then 10 mg/hour for 7 days | • Significant improvement in PaO₂:FiO₂ by day 8 and hospital mortality with hydrocortisone (enrollment suspended at interim analysis)  
• Significant increased survival to hospital discharge in hydrocortisone group (p=0.009) |
| Garcia-Vidal, 2007<sup>22</sup> (Spain) | Retrospective, observational | 308  | Hospitalized patients with severe CAP (PSI IV or V) | 30-day mortality | Methylprednisolone (median dose 45.7 mg/day or equivalent) | • Mortality was similar in both groups (5% no corticosteroids and 7% corticosteroids)  
• Steroids had a protective role (OR 0.287, 95% CI 0.113-0.732)  
• Severity of pneumonia independent factor associated with increased mortality (OR 2.923, 95% CI 1.262-6.770) |
| Snijders, 2010<sup>23</sup> (Netherlands) | Randomized, double-blind, placebo-controlled | 213  | Hospitalized patients with CAP | Clinical cure at day 7 | Prednisolone 40 mg orally or IV daily for 7 days | • No difference in clinical cure at day 7  
• Decline in CRP levels faster in prednisolone group until day 7; CRP higher at day 14  
• More late failures in non-severe CAP in prednisolone group  
• No difference in adverse events |
| Meijvis, 2011<sup>24</sup> (Netherlands) | Randomized, double-blind, placebo-controlled | 304  | Hospitalized patients with confirmed CAP (excluded if direct ICU admission) | Length of hospital stay | Dexamethasone 5 mg IV for 4 days | • Statistically significant difference in median length of hospital stay by 1 day  
• No difference in secondary outcomes of hospital mortality and rates of admission to ICU  
• Greater decline in CRP and IL-6 concentrations in dexamethasone group in first 4 days  
• Hyperglycemia more common in dexamethasone group |
| Nie, 2012<sup>25</sup> | Meta-analysis of 9 RCTs | 1001 | Hospitalized patients with CAP | Mortality | Hydrocortisone, prednisolone, dexamethasone, methylprednisolone  
Duration 1-9 days | • Corticosteroids did not significantly reduce mortality (Peto OR 0.62, 95% CI 0.37-1.04)  
• Subgroup analysis by severity (4 trials, N=214): survival benefit in severe CAP (Peto OR 0.26, 95% CI 0.11-0.64)  
• Subgroup analysis duration of corticosteroids: significant reduction in mortality in prolonged (>5 days) treatment  
• Increased risk of hyperglycemia  
• Potential publication bias |
| Cheng, 2014<sup>18</sup> | Meta-analysis of 4 RCTs | 264  | Hospitalized patients with severe CAP | Hospital mortality (or at longest follow-up time) | Hydrocortisone, prednisolone, and methylprednisolone | • Corticosteroids significantly reduced hospital mortality (Peto OR 0.39, 95% CI 0.17-0.90)  
• Quality of evidence low and downgraded for inconsistency and imprecision  
• Results should be interrupted with caution  
• Moderate heterogeneity among results (I²=46%) |

OR – odds ratio; CI – confidence interval; CRP – C-reactive protein; IL – interleukin; RCT – randomized controlled trial

<table>
<thead>
<tr>
<th>Objective</th>
<th>To assess the effect of corticosteroids in patients with severe community-acquired pneumonia and high inflammatory response</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study Design</td>
<td>Multicenter, randomized, double-blind, placebo-controlled trial</td>
</tr>
</tbody>
</table>
| Population | **Inclusion Criteria:**  
- Aged ≥ 18 years or older  
- Clinical symptoms suggesting CAP (cough, fever, pleuritic chest pain, dyspnea)  
- New chest radiographic infiltrate  
- Met severe CAP criteria (defined by modified ATS criteria or PSI risk class V)  
- C-reactive protein (CRP) level >150 mg/L at admission  

**Exclusion Criteria:**  
- Prior treatment with systemic corticosteroids  
- Nosocomial pneumonia  
- Severe immunosuppression (HIV infection, immunosuppressive condition or medications)  
- Preexisting medical condition with life expectancy <3 months  
- Uncontrolled diabetes mellitus  
- Major gastrointestinal (GI) bleeding within 3 months  
- Condition requiring acute treatment with >1 mg/kg/day methylprednisolone or equivalent  
- H1N1 influenza A pneumonia |
| Outcomes | **Primary outcomes:** rate of treatment failure (early, late, or at both times)  
- Early treatment failure: clinical deterioration within 72 hours of treatment (development of shock, need for invasive mechanical ventilation not present at baseline, or death)  
- Late treatment failure: radiographic progression (increase of ≥50% of pulmonary infiltrates compared with baseline), persistence of severe respiratory failure (pO₂/FiO₂ <200 mm Hg, with respiratory rate ≥30 breaths/min in patients not intubated), development of shock, need for invasive mechanical ventilation not present at baseline, or death between 72 and 120 hours after treatment initiation  
- Secondary outcomes: time to clinical stability, length of ICU and hospital stays, in-hospital mortality  
- Adverse events: hyperglycemia, superinfection, GI bleeding, delirium, acute kidney injury, acute hepatic failure |
| Methods | Three Spanish teaching hospitals – June 2004 to February 2012  
Randomized 1:1 to either methylprednisolone 0.5 mg/kg IV bolus every 12 hours (N=61) or placebo (N=59) for 5 days  
Intervention started within 36 hours of hospital admission  
Antibiotic treatment according to IDSA/ATS CAP guidelines  
Laboratory assessment at presentation: renal and liver functions, electrolytes, blood glucose, CRP, hematology, arterial blood gases  
Biomarker examination: interleukin (IL)-6, IL-8, IL-10, procalcitonin, and CRP levels obtained on first day and after 3 days and 7 days of treatment |
| Statistics | Two-sided type I error of 0.05 and 80% power to detect absolute 20% reduction in treatment failure used to determine sample size of 120  
Pre-specified interim analysis planned at 50% of patient accrual  
Efficacy data analyzed for both intention-to-treat and per-protocol populations  
Sensitivity analysis of primary outcome by logistic regression models  
Primary and secondary outcomes analyzed both with and without an adjustment for potential confounders  
Two predefined covariates: year of admission and the center  
All variables for which there was imbalance between the groups at baseline (p<0.10)  
Statistical tests: X² test, Fisher exact test, t test, nonparametric Mann-Whitney test, Kaplan-Meier method (log-rank test), Cox proportional hazard regression models, logistic regression models  
Calculated 95% confidence intervals  
All tests 2-tailed and significance set at 0.05 |
| Results | 120 patients randomized and 112 (93%) completed study  
Baseline characteristics comparable, except:  
- Lower levels of procalcitonin and IL-10 at day 1 in methylprednisolone group  
- Lower proportion of patients with septic shock in methylprednisolone group |
<table>
<thead>
<tr>
<th>Primary Outcome (Intention-to-treat)</th>
<th>Methylprednisolone (N=61) No. (%)</th>
<th>Placebo (N=59) No. (%)</th>
<th>Difference Between Groups, % (95% CI)</th>
<th>P Value</th>
<th>NNT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment failure</td>
<td>8 (13)</td>
<td>18 (31)</td>
<td>18 (3 to 32)</td>
<td>0.02</td>
<td>6</td>
</tr>
<tr>
<td>Early treatment failure (0-72 h)</td>
<td>6 (10)</td>
<td>6 (10)</td>
<td>0 (-10 to 11)</td>
<td>0.95</td>
<td></td>
</tr>
<tr>
<td>Early mechanical ventilation</td>
<td>4 (7)</td>
<td>5 (8)</td>
<td>2 (-8 to 11)</td>
<td>0.74</td>
<td></td>
</tr>
<tr>
<td>Early septic shock</td>
<td>2 (3)</td>
<td>2 (5)</td>
<td>2 (-5 to 9)</td>
<td>0.68</td>
<td></td>
</tr>
<tr>
<td>Death</td>
<td>2 (3)</td>
<td>2 (3)</td>
<td>0 (-6 to 7)</td>
<td>&gt;0.99</td>
<td></td>
</tr>
<tr>
<td>Late treatment failure (72-120 h)</td>
<td>2 (3)</td>
<td>15 (25)</td>
<td>22 (10 to 34)</td>
<td>0.001</td>
<td>5</td>
</tr>
<tr>
<td>Radiographic progression</td>
<td>1 (2)</td>
<td>9 (15)</td>
<td>14 (4 to 23)</td>
<td>0.007</td>
<td>8</td>
</tr>
<tr>
<td>Respiratory failure</td>
<td>1 (2)</td>
<td>5 (8)</td>
<td>7 (-1 to 15)</td>
<td>0.11</td>
<td></td>
</tr>
<tr>
<td>Late mechanical ventilation</td>
<td>1 (2)</td>
<td>4 (7)</td>
<td>5 (-2 to 12)</td>
<td>0.20</td>
<td></td>
</tr>
<tr>
<td>Late septic shock</td>
<td>0</td>
<td>4 (7)</td>
<td>7 (0 to 13)</td>
<td>0.06</td>
<td></td>
</tr>
<tr>
<td>Death</td>
<td>0</td>
<td>0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Post hoc sub-analysis: late treatment failure excluding radiographic progression</td>
<td>2 (3)</td>
<td>8 (14)</td>
<td>10 (0 to 20)</td>
<td>0.04</td>
<td>10</td>
</tr>
</tbody>
</table>

NNT – number needed to treat

Sensitivity analysis of primary outcome using logistic regression model

<table>
<thead>
<tr>
<th>Primary Outcome</th>
<th>Unadjusted OR or HR (95% CI)</th>
<th>P Value</th>
<th>Adjusted OR or HR (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment failure</td>
<td>0.34 (0.14-0.87)</td>
<td>0.02</td>
<td>0.33 (0.012-0.90)</td>
<td>0.03</td>
</tr>
<tr>
<td>Late treatment failure (72-120 h)</td>
<td>0.10 (0.02-0.46)</td>
<td>0.003</td>
<td>0.09 (0.02-0.47)</td>
<td>0.004</td>
</tr>
<tr>
<td>Radiographic progression</td>
<td>0.09 (0.01-0.76)</td>
<td>0.03</td>
<td>0.09 (0.01-0.78)</td>
<td>0.03</td>
</tr>
</tbody>
</table>

HR – hazard ratio

- Significant difference in time to treatment failure between groups in favor of methylprednisolone (p=0.03)
- Secondary clinical outcomes and adverse events
  - No statistically significant differences observed
- Inflammatory markers
  - At day 3, greater reduction in levels of CRP and IL-10 in methylprednisolone group
  - At day 7, greater reduction in levels of CRP remained in methylprednisolone group
  - Patients with a persistently high inflammatory response at day 7 had higher percentage of treatment failure (p=0.003) and in-hospital mortality (p=0.042)

Authors’ Conclusion
The acute administration of methylprednisolone compared with placebo decreased treatment failure and inflammatory response in patients with severe CAP and high initial inflammatory response. Hypothesize that having less treatment failure could lead to decreased mortality in CAP.

Critique
Strengths:
- Study design
- Intention-to-treat, per-protocol, adjustment for baseline analysis
- All sites used IDSA/ATS guideline for antibiotic therapy
- Evaluated inflammatory response

Limitations:
- Generalizability – limited to severe pneumonia with high inflammatory response
- Small sample size
- Single dose/duration of methylprednisolone studied
- Lower treatment failure in placebo group (31%) compared to study used to calculate sample size – less statistical power
- No long-term follow-up

Application
Corticosteroids may decrease treatment failure in patients with severe CAP and a high inflammatory response. To determine if corticosteroids should be routinely used in patients with CAP, additional well-conducted RCTs with larger sample sizes should be performed.

**Objective**
To assess whether short-term corticosteroid treatment reduces time to clinical stability in patients admitted to the hospital for community-acquired pneumonia

**Study Design**
Double-blind, multicenter, randomized, placebo-controlled trial

**Population**

<table>
<thead>
<tr>
<th>Inclusion Criteria:</th>
<th>Exclusion Criteria:</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Aged 18 years or older</td>
<td>• Active IV drug use</td>
</tr>
<tr>
<td>• Hospital admission with CAP:</td>
<td>• Acute burn injury</td>
</tr>
<tr>
<td>▪ New infiltrate on chest radiograph, and</td>
<td>• GI bleeding within past 3 months</td>
</tr>
<tr>
<td>▪ Presence of ≥1 of the following acute respiratory signs and symptoms: cough, sputum production, dyspnea, core body temperature ≥38.0°C, auscultatory findings of abnormal breathing sounds or rales, leukocyte count &gt;1000 cells/μL or &lt;4000 cells/μL</td>
<td>• Known adrenal insufficiency</td>
</tr>
</tbody>
</table>

**Outcomes**

| • Primary endpoint: time to clinical stability (stable vital signs for ≥24 hours: temperature ≤37.8°C, heart rate ≤100 beats/minute, systolic blood pressure ≥90 mm Hg [≥100 mm Hg if diagnosed with hypertension] without vasopressor support, mental status back to baseline, ability for oral intake, adequate oxygenation on room air [PO2 ≥60 mm Hg or pulse oximetry ≥90%]) | • Secondary endpoints: time to effective hospital discharge, recurrence of pneumonia, hospital readmission, ICU admission, all-cause mortality, duration of total and IV antibiotic therapy, disease activity scores specific to CAP, incidence of complications due to CAP (acute respiratory distress syndrome [ARDS], empyema, persistence of pneumonia), corticosteroid side effects (hyperglycemia, hypertension, delirium, nosocomial infections, weight gain) |

**Methods**

| Seven tertiary care hospitals in Switzerland – December 1, 2009 to May 21, 2014 | Randomized 1:1 to receive either prednisone 50 mg orally daily or placebo for 7 days |
| Variable block sizes of four to six and patients stratified at the time of study entry by study center | Antibiotic therapy according to IDSA/ATS CAP guidelines |
| Patients assessed for clinical stability every 12 hours during hospital stay | Routine laboratory tests of inflammatory markers (procalcitonin, CRP, WBC count) were done on days 1, 3, 5, 7, and before discharge |
| Four blood glucose measurements per day | Follow-up telephone interviews for secondary outcomes after discharge done on day 30 |

**Statistics**

| Calculated needed sample size of 800 patients followed for ≥14 days to achieve statistical power of 85% | Unadjusted HR and 95% CI using Cox proportional hazards regression for primary endpoint |
| Sensitivity analysis: primary outcome analysis repeated on per-protocol population, multivariable Cox proportional hazards model fitted with treatment group and pre-specified potential confounders (patient age and PSI score) | Pre-specified subgroup analysis: patient age, initial CRP concentration, history of COPD, PSI class, blood culture positivity |
| Secondary endpoints: calculated unadjusted and adjusted (for patient age and PSI score) estimate of the effect size and corresponding 95% CIs using linear, logistic, or Cox proportional hazards regression | Two-sided 95% CIs and two-sided 5% significance level |

**Results**

| 802 eligible patients initially enrolled: 392 prednisone group and 393 placebo group |
| Baseline characteristics well balanced (high burden of comorbidities: diabetes, COPD, chronic heart failure, chronic renal insufficiency; approximately half patients in high-risk PSI classes IV and V) |

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Prednisone (N=392)</th>
<th>Placebo (N=393)</th>
<th>HR, OR, or Difference (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary endpoint</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time to clinical stability (days), intention-to-treat</td>
<td>3.0 (2.5-3.4)</td>
<td>4.4 (4.0-5.0)</td>
<td>HR: 1.33 (1.15 to 1.50)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Time to clinical stability (days), per-protocol</td>
<td>3.0 (2.5-3.2)</td>
<td>4.4 (4.0-5.0)</td>
<td>HR: 1.35 (1.16 to 1.56)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

Klem blister | 10
**Secondary endpoints**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Prednisone (N=392)</th>
<th>Placebo (N=393)</th>
<th>OR or Difference (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complications due to CAP</td>
<td>11 (3%)</td>
<td>22 (6%)</td>
<td>0.49 (0.23 to 1.02)</td>
<td>0.056</td>
</tr>
<tr>
<td>Weight change (kg)</td>
<td>-1.0 (-3.0 to 1.0)</td>
<td>-1.0 (-3.0 to 0.4)</td>
<td>Difference: 0.34 (-0.56 to 1.25)</td>
<td>0.46</td>
</tr>
<tr>
<td>Adverse events compatible with corticosteroids, any</td>
<td>96 (24%)</td>
<td>61 (16%)</td>
<td>1.77 (1.24 to 2.52)</td>
<td>0.0020</td>
</tr>
<tr>
<td>In-hospital hyperglycemia needing insulin treatment</td>
<td>76 (19%)</td>
<td>43 (11%)</td>
<td>1.96 (1.31 to 2.93)</td>
<td>0.0010</td>
</tr>
<tr>
<td>Other adverse event, any</td>
<td>20 (5%)</td>
<td>34 (9%)</td>
<td>0.57 (0.32 to 1.00)</td>
<td>0.052</td>
</tr>
</tbody>
</table>

Data are median (IQR) or number (%)

**Complications and adverse events until day 30**

- No evidence of effect modification in different pre-specified subgroups
- CRP concentrations significantly lower in prednisone group than in placebo group on days 3, 5, and 7

**Authors’ Conclusion**

Findings support the hypothesis that administration of corticosteroids modulates the immune response and thereby shortens time to clinical stability and length of hospital stay. Results confirm data of various clinical trials, systematic reviews, and meta-analyses showing a beneficial effect of corticosteroids in CAP.

**Critique**

**Strengths:**
- Study design
- Largest and most conclusive randomized placebo-controlled trial to date
- All severity classes of CAP included
- Sensitivity analysis
- 30-day follow-up
- Oral prednisone – ease of administration

**Limitations:**
- Limited generalizability to only hospitalized patients
- Not powered for mortality
- Slightly smaller sample size than predicted
- Limitations of primary endpoint of time to clinical stability (combined endpoint including several parameters)
- Corticosteroid-induced hyperglycemia may have led to un-blinding

**Application**

Corticosteroids appear to reduce the time to clinical stability and may improve the clinical course of disease in patients hospitalized with CAP. Hyperglycemia is the most common adverse event associated with short-term corticosteroid treatment.
Objective
To examine the effect of adjunctive corticosteroid therapy on mortality, morbidity, and duration of hospitalization in patients with community-acquired pneumonia

Study Design
Systematic review and meta-analysis of randomized controlled trials

Population
Inclusion Criteria:
• Adults with CAP assigned to oral or IV corticosteroid therapy versus placebo or no treatment
• Studies reported on ≥1 outcome of interest

Exclusion Criteria:
• Ventilator-associated pneumonia, aspiration pneumonia, or Pneumocystis jiroveci pneumonia
• Studies limited to patients with COPD

Outcomes
All-cause mortality, need for mechanical ventilation, ICU admission, development of ARDS, duration of hospitalization, time to clinical stability

Methods
• Previous Cochrane review with similar inclusion criteria identified studies up to December 2010
• MEDLINE, EMBASE, and the Cochrane Central Register of Controlled Trials searched from January 1, 2010 to May 24, 2015 using the Medical Subject Heading terms “pneumonia” and “corticosteroids”
• If study reported outcomes at more than one time point, data was abstracted closest to 30 days from randomization
• Grading of Recommendations Assessment, Development, and Evaluation (GRADE) system used to assess certainty of evidence for each outcome and for entire body of evidence

Statistics
• Random-effects models (Mantel-Haenszel risk ratios and mean differences)
• Nonparametric data converted to means and standard deviations
• Sensitivity analysis: omitting studies in which means were estimated from medians and omitting one study that was stopped early for a large effect
• Heterogeneity assessed using visual inspection of the results and the I² statistic
• 95% confidence intervals calculated

Results
Thirteen RCTs identified (nine studies not included in the previous review)
Sample sizes ranged from 30-784 hospitalized patients
Corticosteroids: dexamethasone, prednisone, prednisolone, methylprednisolone, or hydrocortisone
Duration of treatment ranged from one dose to 10 days
Follow-up ranged from in-hospital to 60 days from enrollment
Studies often excluded patients at high risk for adverse effects from corticosteroids (GI hemorrhage within 3 months, immunosuppression, pregnant women)

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Corticosteroids (n/N)</th>
<th>Control (n/N)</th>
<th>RR (95% CI)</th>
<th>I² (%)</th>
<th>Certainty of Evidence</th>
<th>NNT</th>
</tr>
</thead>
<tbody>
<tr>
<td>All-cause mortality</td>
<td>7.9% (79/997)</td>
<td>5.3% (52/977)</td>
<td>0.67 (0.45-1.01)</td>
<td>6</td>
<td>Moderate</td>
<td></td>
</tr>
<tr>
<td>Mechanical ventilation</td>
<td>3.1% (17/550)</td>
<td>5.7% (29/510)</td>
<td>0.45 (0.26-0.79)</td>
<td>0</td>
<td>Moderate</td>
<td>39</td>
</tr>
<tr>
<td>ICU admission</td>
<td>5.3% (25/476)</td>
<td>7.6% (36/474)</td>
<td>0.69 (0.46-1.03)</td>
<td>0</td>
<td>Moderate</td>
<td></td>
</tr>
<tr>
<td>ARDS</td>
<td>0.42% (2/473)</td>
<td>3.0% (14/472)</td>
<td>0.24 (0.10-0.56)</td>
<td>0</td>
<td>Moderate</td>
<td>39</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Corticosteroids</th>
<th>Control</th>
<th>Mean Difference, days (95% CI)</th>
<th>I² (%)</th>
<th>Certainty of Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration of hospitalization</td>
<td></td>
<td></td>
<td>-2.96 (-5.18 to -0.75)</td>
<td>94</td>
<td>High</td>
</tr>
<tr>
<td>Duration of hospitalization</td>
<td>7.9 days</td>
<td>9.1 days</td>
<td>-1.00 (-1.79 to -0.21)</td>
<td>0</td>
<td>High</td>
</tr>
<tr>
<td>Time to Clinical Stability</td>
<td>3.5 days</td>
<td>4.7 days</td>
<td>-1.22 (-2.08 to -0.35)</td>
<td>38</td>
<td>High</td>
</tr>
</tbody>
</table>
Subgroup analysis by pneumonia severity

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Corticosteroids (n/N)</th>
<th>Control (n/N)</th>
<th>RR (95% CI)</th>
<th>I² (%)</th>
<th>NNT</th>
</tr>
</thead>
<tbody>
<tr>
<td>All-cause mortality</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Severe pneumonia (6 studies, N=388)</td>
<td>7.4% (16/215)</td>
<td>22% (38/173)</td>
<td>0.39 (0.20-0.77)</td>
<td>0</td>
<td>7</td>
</tr>
<tr>
<td>Not severe pneumonia (6 studies, N=1586)</td>
<td>4.7% (36/762)</td>
<td>5.0% (41/824)</td>
<td>1.00 (0.79-1.26)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Mechanical ventilation</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Severe pneumonia (3 studies, N=230)</td>
<td>11.1% (15/135)</td>
<td>18.9% (18/95)</td>
<td>0.54 (0.50-0.58)</td>
<td>0</td>
<td>13</td>
</tr>
<tr>
<td>Not severe pneumonia (2 studies, N=830)</td>
<td>0.48% (2/415)</td>
<td>2.7% (11/415)</td>
<td>0.18 (0.08-0.43)</td>
<td>0</td>
<td>45</td>
</tr>
</tbody>
</table>

Adverse events

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Corticosteroids (n/N)</th>
<th>Control (n/N)</th>
<th>RR (95% CI)</th>
<th>I² (%)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyperglycemia requiring treatment</td>
<td>15.2% (119/784)</td>
<td>8.7% (65/750)</td>
<td>1.49 (1.01-2.19)</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal hemorrhage</td>
<td>1.1% (7/628)</td>
<td>1.7% (10/595)</td>
<td>0.82 (0.33-1.62)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Severe neuropsychiatric complications</td>
<td>1.8% (11/602)</td>
<td>1.3% (8/615)</td>
<td>1.65 (0.88-3.08)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Rehospitalization</td>
<td>7.2% (39/543)</td>
<td>6.3% (35/546)</td>
<td>1.12 (0.59-2.13)</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>

*High certainty of evidence

- NNH for hyperglycemia requiring treatment: 16
- Subgroup analyses: risk of bias, year of publication, severity of pneumonia at enrollment, duration of corticosteroid therapy did not show a consistent interaction across outcomes
- Sensitivity analyses: omission of one study that was stopped early for benefit had no appreciable effect on the results; omission of studies in which means were estimated from median values for continuous outcomes had negligible effect on the results

Authors’ Conclusion

Results provide high-quality evidence for the benefits of adjunctive corticosteroids in CAP and decision makers should strongly consider the use of corticosteroids in patients hospitalized with CAP, particularly in those who are more severely affected. Overall certainty of available evidence rated as high for the benefit of adjunctive corticosteroids.

Critique

Strengths:
- Assessed eligibility and risk of bias in duplicate
- Rigorous literature search
- Applied GRADE system to evaluate certainty of evidence
- Subgroup and sensitivity analyses

Limitations:
- Use of various corticosteroids, routes of administration, doses, and treatment duration
- Generalizability
- Some outcomes with small number of events (need for mechanical ventilation, admission to ICU, ARDS)
- Publication bias could not be ruled out
- High degree in heterogeneity in primary analysis of duration of hospitalization
- “Rapid meta-analysis” method new and not yet validated

Application

Corticosteroids may benefit several outcomes in CAP, with the major adverse event in short-term treatment being hyperglycemia. Larger RCTs could improve certainty of the benefit of adjunctive corticosteroids in CAP. Additional trials are needed to determine optimal corticosteroid, dose, duration of treatment, and the ideal patient population.
FUTURE STUDIES

I. Extended Steroid in CAP(e) (ESCAPE)30
   A. Objective: to determine if providing early treatment with methylprednisolone will improve survival in critically ill patients with severe CAP
   B. Primary outcome: all-cause mortality at 60 days
   C. Intervention: methylprednisolone 40 mg/day for 7 days, then 20 mg/day for 7 days, then 6 days of tapering dose (12 mg/day and 4 mg/day)
   D. Currently recruiting participants
      1. Estimated completion date: January 2018

II. Santeon-CAP; Dexamethasone in Community-acquired Pneumonia31
   A. Objective: to investigate the beneficial effects of adjunctive dexamethasone in patients hospitalized for CAP with an aim to assess which patients benefit the most from treatment
   B. Primary outcome: length of hospital stay
   C. Intervention: dexamethasone 6 mg daily for 4 days
   D. Currently recruiting participants
      1. Estimated completion date: December 2015

III. Corticosteroid Therapy for Severe Community-Acquired Pneumonia32
    A. Objective: to assess the efficacy of adjunctive methylprednisolone in patients with CAP
    B. Primary outcome: all-cause mortality at 30 days
    C. Intervention: methylprednisolone 80 mg/day for 3 days, then 40 mg/day for 3 days
    D. Currently recruiting participants
       1. Estimated completion date: May 2017

IV. Community-Acquired Pneumonia: Evaluation of Corticosteroids (CAPE_COD)33
    A. Objective: to determine if corticosteroids improve survival in critically-ill patients with severe CAP
    B. Primary outcome: all-cause mortality at 28 days
    C. Intervention: hydrocortisone 200 mg/day by continuous IV infusion for 4 or 7 days, then 100 mg/day for 2 or 4 days, and then 50 mg/day for 2 or 3 days (duration chosen upon patient initial improvement)
    D. Not yet open for recruitment
       1. Estimated completion date: December 2018

V. Corticosteroids in Community-acquired Pneumonia34
    A. Objective: to determine the efficacy of the addition of corticosteroid therapy to antibiotics in children hospitalized with CAP
    B. Primary outcome: length of hospital stay
    C. Intervention: dexamethasone 0.6 mg/kg/day or methylprednisolone 1 mg/kg/day
    D. Not yet open for recruitment
       1. Estimated completion date: March 2017

CONCLUSION AND RECOMMENDATIONS

I. Should adjunctive corticosteroids be used in the treatment of community-acquired pneumonia?
   A. Numerous studies investigating the potential benefit of adjunctive corticosteroid therapy in the treatment of CAP
      1. Most are small, single site studies
      2. Various outcomes studied
      3. Various anti-inflammatory agents, doses, and duration of treatment
      4. Many studies showed a benefit with corticosteroids
         a. Limited studies powered to show mortality benefit
      5. Hyperglycemia most common adverse effect observed
      6. Limitations with earlier meta-analyses
         a. Mortality benefit only in subgroup analysis of severe CAP (N=214)25
            i. Possible publication bias
         b. Reduction in mortality in meta-analysis of only four trials and quality of evidence down-graded due to moderate heterogeneity18
            i. Results should be interrupted with caution

Klembith | 14
B. Recent RCTs and meta-analysis confirm beneficial effects of corticosteroids as adjunctive treatment in CAP with limited adverse events
   1. Positive outcomes
      a. Decrease in treatment failure
      b. Decrease time to clinical stability by 1 day
         i. May translate to decreased length of hospital stay
         (i) Economic benefit
         (ii) Patient at decreased risk of nosocomial infections and deep vein thrombosis
   2. Mortality benefit observed in meta-analysis subgroup analysis of patients with severe CAP

II. Additional areas of research
A. Specific population with potential for the most benefit from corticosteroid therapy
   1. Pneumonia severity
   2. Outpatient
   3. Elderly
B. Optimal corticosteroid agent, dose, and duration of treatment

III. Clinical recommendations
A. Further studies are needed before corticosteroids should be broadly recommended as adjunctive treatment of CAP
B. Adjunctive corticosteroids should be considered in patients hospitalized with severe CAP
   1. PSI risk class IV and V or CURB-65 score ≥2
   2. Prednisone 50 mg orally daily or methylprednisolone 0.5 mg/kg IV every 12 hours
   3. Treatment duration of 5-7 days
C. Evaluate patient-specific risks versus benefits of corticosteroid therapy

REFERENCES

Klembith | 15


<table>
<thead>
<tr>
<th>Table 4. Abbreviations</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>ARDS</td>
<td>Acute respiratory distress syndrome</td>
</tr>
<tr>
<td>BTS</td>
<td>British Thoracic Society</td>
</tr>
<tr>
<td>BUN</td>
<td>Blood urea nitrogen</td>
</tr>
<tr>
<td>CAP</td>
<td>Community-acquired pneumonia</td>
</tr>
<tr>
<td>CI</td>
<td>Confidence interval</td>
</tr>
<tr>
<td>COPD</td>
<td>Chronic obstructive pulmonary disease</td>
</tr>
<tr>
<td>COX-2</td>
<td>Cyclooxygenase-2</td>
</tr>
<tr>
<td>cPLA2α</td>
<td>Cytosolic phospholipase A2α</td>
</tr>
<tr>
<td>CRH</td>
<td>Corticotropin-releasing hormone</td>
</tr>
<tr>
<td>CRP</td>
<td>C-reactive protein</td>
</tr>
<tr>
<td>ED</td>
<td>Emergency department</td>
</tr>
<tr>
<td>ERS/ESCMID</td>
<td>European Respiratory Society/European Society of Clinical Microbiology and Infectious Diseases</td>
</tr>
<tr>
<td>GI</td>
<td>Gastrointestinal</td>
</tr>
<tr>
<td>GRADE</td>
<td>Grading of Recommendations Assessment, Development, and Evaluation</td>
</tr>
<tr>
<td>HIV</td>
<td>Human immunodeficiency virus</td>
</tr>
<tr>
<td>HR</td>
<td>Hazard ratio</td>
</tr>
<tr>
<td>ICU</td>
<td>Intensive care unit</td>
</tr>
<tr>
<td>IDSA/ATS</td>
<td>Infectious Diseases Society of America/American Thoracic Society</td>
</tr>
<tr>
<td>IL</td>
<td>Interleukin</td>
</tr>
<tr>
<td>IQR</td>
<td>Interquartile range</td>
</tr>
<tr>
<td>IV</td>
<td>Intravenous</td>
</tr>
<tr>
<td>MAPK</td>
<td>Mitogen-activated protein kinase</td>
</tr>
</tbody>
</table>
APPENDICES

Appendix A: Clinical Indications for Extensive Diagnostic Testing

<table>
<thead>
<tr>
<th>Indication</th>
<th>Blood culture</th>
<th>Sputum culture</th>
<th>Legionella UAT</th>
<th>Pneumococcal UAT</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>ICU admission</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Failure of outpatient antibiotic therapy</td>
<td></td>
<td></td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Cavitary infiltrates</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Leukopenia</td>
<td>X</td>
<td></td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Active alcohol abuse</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Chronic severe liver disease</td>
<td>X</td>
<td></td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Severe obstructive/structural lung disease</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Asplenia (anatomic or functional)</td>
<td>X</td>
<td></td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Recent travel (within past 2 weeks)</td>
<td></td>
<td></td>
<td>X</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Positive Legionella UAT result</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive pneumococcal UAT result</td>
<td>X</td>
<td></td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pleural effusion</td>
<td>X</td>
<td>X</td>
<td></td>
<td>X</td>
<td></td>
</tr>
</tbody>
</table>

UAT – urinary antigen test

Appendix B: Pneumonia Severity Index for Community-Acquired Pneumonia

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographics</td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>Age (years)</td>
</tr>
<tr>
<td>Women</td>
<td>Age (years) – 10</td>
</tr>
<tr>
<td>Nursing home resident</td>
<td>+10</td>
</tr>
<tr>
<td>Comorbidities</td>
<td></td>
</tr>
<tr>
<td>Neoplasm</td>
<td>+30</td>
</tr>
<tr>
<td>Liver disease</td>
<td>+20</td>
</tr>
<tr>
<td>Heart Failure</td>
<td>+10</td>
</tr>
<tr>
<td>Stroke</td>
<td>+10</td>
</tr>
<tr>
<td>Renal failure</td>
<td>+10</td>
</tr>
<tr>
<td>Physical exam</td>
<td></td>
</tr>
<tr>
<td>Altered mental status</td>
<td>+20</td>
</tr>
<tr>
<td>Respiratory rate ≥ 30 breaths/min</td>
<td>+20</td>
</tr>
<tr>
<td>Systolic blood pressure &lt; 90 mm Hg</td>
<td>+20</td>
</tr>
<tr>
<td>Temperature &lt;35°C or ≥40°C</td>
<td>+15</td>
</tr>
<tr>
<td>Pulse ≥125 beats/min</td>
<td>+10</td>
</tr>
</tbody>
</table>
Laboratory and radiographic findings

<table>
<thead>
<tr>
<th>Test</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arterial pH &lt;7.35</td>
<td>+30</td>
</tr>
<tr>
<td>Blood urea nitrogen &gt;30 mg/dL</td>
<td>+20</td>
</tr>
<tr>
<td>Sodium &lt;130 mmol/L</td>
<td>+20</td>
</tr>
<tr>
<td>Glucose ≥250 mg/dL</td>
<td>+10</td>
</tr>
<tr>
<td>Hematocrit &lt;30%</td>
<td>+10</td>
</tr>
<tr>
<td>Partial pressure of arterial oxygen &lt;60 mm Hg</td>
<td>+10</td>
</tr>
<tr>
<td>Pleural effusion</td>
<td>+10</td>
</tr>
</tbody>
</table>

Appendix C: Empirical Antimicrobial Treatment for CAP

<table>
<thead>
<tr>
<th>Patient Characteristics</th>
<th>Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Outpatient and previously healthy and no use of antibiotics in last 3 months</td>
<td>• Macrolide</td>
</tr>
<tr>
<td></td>
<td>• Alternative: doxycycline</td>
</tr>
<tr>
<td>Outpatient with presence of comorbidities (chronic heart, lung, or renal disease; diabetes; alcoholism; malignancies; asplenia; immunosuppressing conditions; use of antibiotics within past 3 months)</td>
<td>• Respiratory fluoroquinolone (levofoxacin, moxifloxacin)</td>
</tr>
<tr>
<td></td>
<td>• Beta-lactam plus macrolide</td>
</tr>
<tr>
<td>Outpatient in regions with &gt;25% of infections with high-level (MIC ≥ 16µL/mL) macrolide-resistant S. pneumoniae</td>
<td>Consider respiratory fluoroquinolone or beta-lactam plus macrolide</td>
</tr>
<tr>
<td>Inpatient, non-ICU</td>
<td>• Respiratory fluoroquinolone</td>
</tr>
<tr>
<td></td>
<td>• Beta-lactam plus macrolide</td>
</tr>
<tr>
<td>Inpatient, ICU</td>
<td>Beta lactam (cefotaxime, ceftriaxone, or ampicillin-sulbactam) plus either azithromycin or respiratory fluoroquinolone</td>
</tr>
</tbody>
</table>

Appendix D: Glucocorticoid Anti-Inflammatory Mechanisms of Action

![Glucocorticoid Mechanisms Diagram]
# Appendix E: Glucocorticoid Pharmacology

<table>
<thead>
<tr>
<th>Glucocorticoid</th>
<th>Dosing</th>
<th>Routes of administration</th>
<th>Pharmacokinetics</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hydrocortisone</td>
<td>15-240 mg Q12h (No dosage adjustments)</td>
<td>PO, IM, IV</td>
<td>• Absorption: rapid&lt;br&gt;• Metabolism: hepatic (minor substrate CYP3A4, P-glycoprotein substrate)&lt;br&gt;• Half-life: 8-12 hours&lt;br&gt;• Excretion: urine</td>
<td>Off-label septic shock indication</td>
</tr>
<tr>
<td>Cortisone acetate</td>
<td>25-300 mg/day (PO) (No dose adjustments, use with caution in renal and hepatic impairment)</td>
<td>PO, IM</td>
<td>• Absorption: readily&lt;br&gt;• Distribution: muscles, liver, skin, intestines, kidneys&lt;br&gt;• Metabolism: hepatic to active metabolite hydrocortisone (cortisol)&lt;br&gt;• Bioavailability: interindividual variability: 43.7%&lt;br&gt;• Half-life elimination: 0.5 hours&lt;br&gt;• Excretion: urine and feces</td>
<td></td>
</tr>
<tr>
<td>Prednisone</td>
<td>5-60 mg daily (No dose adjustments)</td>
<td>PO</td>
<td>• Absorption: 50-90%&lt;br&gt;• Metabolism: hepatic to prednisolone (minor CYP3A4 substrate, weak/moderate CYP2C19 inducer)&lt;br&gt;• Half-life: 2-3 hours&lt;br&gt;• Excretion: urine</td>
<td>Off-label COPD exacerbation indication</td>
</tr>
<tr>
<td>Prednisolone</td>
<td>5-60 mg daily (No dosage adjustments, use with caution in renal impairment)</td>
<td>PO, IM, IV, intra-articular, intradermal, soft tissue injection</td>
<td>• Metabolism: primary hepatic (minor CYP3A4 substrate), also metabolized in most tissues&lt;br&gt;• Half-life elimination: 3.6 hours&lt;br&gt;• Excretion: primarily urine</td>
<td>Off-label COPD exacerbation indication</td>
</tr>
<tr>
<td>Methylprednisolone</td>
<td>• Oral: 2-60 mg/day&lt;br&gt;• IM (sodium succinate): 10-80 mg/day&lt;br&gt;• IM (acetate): 10-80 mg Q1-2 weeks&lt;br&gt;• IV (sodium succinate): 10-40 mg over several minutes and repeated IV or IM at intervals depending on clinical response (No dosage adjustments, use caution in renal failure)</td>
<td>PO, IM, IV</td>
<td>• Distribution: 0.7-1.5 L/kg&lt;br&gt;• Metabolism: minor CYP3A4 substrate, weak CYP2C8 inhibitor&lt;br&gt;• Half-life elimination: 3-2.5 hours (reduced in obese)&lt;br&gt;• Excretion: reduced in obese</td>
<td>Off-label COPD exacerbation indication</td>
</tr>
<tr>
<td>Dexamethasone</td>
<td>• Oral, IM, IV: 0.75-9 mg/day Q6-12h (in divided doses)&lt;br&gt;• Intra-articular, intralesional, soft tissue: 0.4-6 mg/day (No dosage adjustments, use caution in renal impairment)</td>
<td>PO, IM, IV, intra-articular, intradermal, soft tissue injection</td>
<td>• Absorption: oral 61-86%&lt;br&gt;• Metabolism: hepatic (major CYP3A4 substrate, P-glycoprotein substrate and inhibitor, weak/moderate CYP2A6, CYP2B6, CYP2C9 inducer, weak CYP3A4 inducer, P-glycoprotein and UGT1A1 inducer&lt;br&gt;• Half-life elimination: oral ~4 hours; IV 1-5 hours&lt;br&gt;• Excretion: urine</td>
<td></td>
</tr>
</tbody>
</table>