Roid (all the) Rage:
Corticosteroids in Community Acquired Pneumonia

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Agenda

- Brief history of pneumonia and treatment
- Review of potential outcomes
- Recent randomized control trials
- 2015 Meta-analysis
- Conclusions & Questions
S. Pneumonia discovered

Antipneumococcal serum created
Mortality reduced from 25% to 7.5%

First antibiotic agent, Sulfapyridine, created
Used to treat Winston Churchill’s bacterial PNA in 1942

S. Pneumonia resistance to Penicillin

PPV vaccine created

PCV vaccine created

PNA top two leading cause of death

1 Late 1800s/Early 1900s
2 1881
3 1913
4 1940s
5 1940s+
6 1977
7 2000

PNEUMONIA THROUGH TIME
Discussion of adjunct corticosteroids in CAP begins

Reduction in in-hospital mortality for severe CAP (Small RCT)

No benefit to adjunct corticosteroids. Increased recurrence rate

IV Dexamethasone with significant reduction in hospital LOS

Three meta-analyses. Two find mortality benefit in severe CAP. One finds no mortality benefit.
PNEUMONIA IN 2015

Feb 2015
Torres et al. *JAMA*. Methylprednisolone in severe CAP + elevated CRP.\(^9\)

Apr 2015
Blum et al. *The Lancet*. Prednisone adjunct in CAP.\(^10\)

Oct 2015
Reed et al. *Ann Int Med*. Meta-analysis of corticosteroids in hospitalized CAP. \(^11\)
Do Corticosteroids Improve CAP Outcomes?

SIMPLE QUESTION

COMPLEX ANSWERS

MORTALITY BENEFIT?

LENGTH OF STAY?

ARDS RATES?

RADIOGRAPHIC PROGRESSION?

VENTILATION RATES?
SHOULD WE JUST FOCUS ON SEVERE CAP?
Torres et al. (JAMA, Feb 2015)

- Multicenter, randomized, double-blind control trial of 120 adult patients in Spain

- **Inclusion Criteria:** Both “severe” CAP and CRP > 150 mg/L at admission.
  - Severe criteria = ATS criteria or Risk Class V for PSI

- **Treatment:** IV Methylprednisolone 0.5mg/kg q12h for 5 days within 36 hours of admission

- **Primary Outcome:** “Treatment Failure”
  - Composite of early and late failure
    - Development of shock
    - Need for invasive mechanical ventilation not present at baseline
    - Death within 72 hours of treatment
    - Radiographic progression
    - Persistence of respiratory failure
Torres et al. (JAMA, Feb 2015)

• Results:
  • Less treatment failure in methylprednisolone group
    • 13% vs 31% (p=0.02) (95% CI 0.14-0.87)
  • No difference in in-hospital mortality
    • 10% vs 15% (p=.37) (95% CI, -6% to 17%)
• Weaknesses:

- Treatment failure outcome almost exclusively powered by radiographic progression.
- Only 23-24% of treatment-control groups treated with macrolide.
- Only 57% of eligible patients meeting severe CAP criteria had CRP > 15.
- Eligibility not specific enough?

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**Table 2. Clinical Outcomes Using Descriptive Statistics for the Intention-to-Treat and Per-Protocol Populations**

<table>
<thead>
<tr>
<th></th>
<th>Intention-to-Treat Population</th>
<th>Per-Protocol Population</th>
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<tbody>
<tr>
<td></td>
<td>Methylprednisolone Group</td>
<td>Placebo Group</td>
</tr>
<tr>
<td></td>
<td>(n = 61)</td>
<td>(n = 59)</td>
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<tr>
<td>Primary Clinical Outcome</td>
<td></td>
<td></td>
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<tr>
<td>Treatment failure, No. (%)</td>
<td>8 (13)</td>
<td>18 (31)</td>
</tr>
<tr>
<td>Early treatment failure (0-72 h), No. (%)</td>
<td>6 (10)</td>
<td>6 (10)</td>
</tr>
<tr>
<td>Early mechanical ventilation</td>
<td>4 (7)</td>
<td>5 (8)</td>
</tr>
<tr>
<td>Early septic shock</td>
<td>2 (3)</td>
<td>3 (5)</td>
</tr>
<tr>
<td>Death</td>
<td>2 (3)</td>
<td>3 (3)</td>
</tr>
<tr>
<td>Late treatment failure (72-120 h), No. (%)</td>
<td>2 (3)</td>
<td>15 (25)</td>
</tr>
<tr>
<td>Respiratory failure</td>
<td>1 (2)</td>
<td>9 (15)</td>
</tr>
<tr>
<td>Late mechanical ventilation</td>
<td>1 (2)</td>
<td>5 (8)</td>
</tr>
<tr>
<td>Late septic shock</td>
<td>0</td>
<td>4 (7)</td>
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<tr>
<td>Death</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Secondary Clinical Outcomes</td>
<td></td>
<td></td>
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<tr>
<td>Time to clinical stability, median (IQR), d</td>
<td>4 (3 to 6)</td>
<td>5 (3 to 7)</td>
</tr>
<tr>
<td>Length of stay, median (IQR), d</td>
<td>11 (7 to 14)</td>
<td>10.5 (6 to 15)</td>
</tr>
<tr>
<td>ICU stay, No. (%)</td>
<td>5 (3 to 8)</td>
<td>6 (4 to 8)</td>
</tr>
<tr>
<td>In-hospital mortality, No. (%)</td>
<td>6 (10)</td>
<td>9 (14)</td>
</tr>
</tbody>
</table>
PNEUMONIA IN 2015

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Oct 2015
Reed et al. *Ann Int Med*. Meta-analysis of corticosteroids in hospitalized CAP. 11
BLUM et al. (Lancet, April 2015)

• Multicenter, randomized, double-blind control trial of 785 adult patients in Switzerland

• **Inclusion Criteria:** Infiltrate on CXR + clinical finding

• **Treatment:** PO prednisone 50mg daily for 7 days

• **Primary Outcome:** “Clinical Stability”
  • Time until stable vital signs for 24 hours
BLUM et al. (Lancet, April 2015)

• Results:
  • Shorter median time to clinic stability
    • 3 days vs 4.4 days (95% CI 1.15-1.50, p < 0.0001)
  • Shorter time to hospital discharge
    • 6 days vs 7 days (P=0.012)
  • No difference in all-cause mortality, rates of recurrence, re-admissions, and ICU admissions.
  • No effect modification based on severity
PNEUMONIA IN 2015

Feb 2015
Torres et al. *JAMA*. Methylprednisolone in severe CAP + elevated CRP.⁹

Apr 2015
Blum et al. *The Lancet*. Prednisone adjunct in CAP.¹⁰

Oct 2015
Reed et al. *Ann Int Med*. Meta-analysis of corticosteroids in hospitalized CAP.¹¹
SIEMIENIUK et al. (Ann Int Med, October 2015)

• Meta-analysis of 13 RCTS evaluating systemic corticosteroids in 2,005 hospitalized adults with CAP

• Possible reduction in mortality with corticosteroid use that is driven by subgroups evaluating severe pneumonia.
  • Large magnitude of effect
  • Small interaction P value (0.010)

• Decrease in hospital stay (1 day), time to clinical stability (1.22 days), ARDS (RR 0.24), and need for ventilation (RR 0.45)
Effect lost if stratifying studies by degree of bias

Based on differences between studies and not difference within studies

Largely driven by small study stopped early for benefit

No consistency in subgroup effect with related outcomes (Mechanical ventilation and ARDS)

SIEMIENIUK et al. (Ann Int Med, October 2015)
CONCLUSIONS

• Many clinically relevant benefits to adjunctive corticosteroid use in CAP that likely outweigh hyperglycemia

• Mortality benefit still questionable. Unlikely to see in less severe cases but still remains to be seen in severe cases.

• Dose and duration variable – more answers in 2018 (ESCAPe Trial)
References


9. Effect of Corticosteroids on Treatment Failure Among Hospitalized Patients With Severe Community-Acquired Pneumonia and High Inflammatory ResponseA Randomized Clinical Trial FREE Antoni Torres, MD, PhD1,2,3,4; Oriol Sibila, MD, PhD1,2,3; Miquel Ferrer, MD, PhD1,2,3; Eva Poverino, MD, PhD1,2,3; Rosario Menendez, MD, PhD1,2,3; Josep Mensa, MD, PhD1,2,3; Albert Gabarrus, MSc1,2,3; Jacobo Sellares, MD, PhD1,2,3; Marcos I. Restrepo, MD, MSc1,2,3; Antonio Anzueto, MD, PhD1,2,3; Michael S. Niederman, MD1,2; Carles Agustí, MD, PhD1,2,3 JAMA. 2015;313(7):677-686. doi:10.1001/jama.2015.88.

QUESTIONS?