RATIONALE FOR PROLONGED CORTICOSTEROID TREATMENT [CST] IN ARDS CAUSED BY COVID-19

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Disclosure - Conflict of Interest

☐ None
☐ Academic Bias

Academic Freedom Saves Lives  DOI: 10.13140/RG.2.1.3936.1762
COVID-19  A National Emergency

- USA TODAY – March 18, 2020 “Too many coronavirus patients, too few ventilators: Outlook in US could get bad, quickly ... As we face potentially 'the largest workforce crisis in our generation,' hospitals are bracing for ventilator shortages amid the coronavirus outbreak.”

- Any intervention directed at decreasing MV dependence and mortality in COVID-19 patients could have a significant impact on public health

1. Interferon regulator factors:
   - Type I and III interferon...
   - INF-γ decreased viral replication

2. Nuclear factor-kB:
   - Influx activated infl. cells [PMN, mono, macrophages]
   - TNF-α, IL-1β, IL-6, ...

ACE2 expressing type II epithelial cells ► RNA viral recognition by intracellular pattern receptors ► transcription activation: [1] IRFs and [2] NF-kB

Suppressed anti-viral defense and amplified inflammation

Optimal response

Dysregulated response

Suppressed ► Viral replication

Amplified

1. Interferon regulator factors: Type I and III interferon ...
   - INF-γ decreased viral replication

2. Nuclear factor-kB: influx activated infl. cells [PMN, mono, macrophages]
   - TNF-α, IL-1β, IL-6, ...

CYTOKINE STORM ► ARF ► MV
   - Macrophage activation
   - Immune dysregulation

COVID-19 Illness in Native and Immunosuppressed States: A Clinical-Therapeutic Staging Proposal

- Exhausted anti-viral defense
- Dysregulated inflammation

**Stage I (Early Infection)**
- Viral response phase
  - Clinical Symptoms: Mild constitutional symptoms, Fever >99.6°F, Dry Cough, diarrhea, headache
  - Clinical Signs: Lymphopenia, increased prothrombin time, increased D-Dimer and LDH (mild)

**Stage II (Pulmonary Phase)**
- Host inflammatory response phase
  - IIA: without hypoxia
  - IIB: with hypoxia (PaO2/FIO2<300mmHg)
  - Clinical Symptoms: Shortness of Breath, Hypoxia
  - Clinical Signs: Abnormal chest imaging, Transaminitis, Low-normal procalcitonin

**Stage III (Hyperinflammation Phase)**
- HLH
  - Clinical Symptoms: ARDS, SIRS/Shock, Cardiac Failure
  - Clinical Signs: Elevated inflammatory markers (CRP, LDH, IL-6, D-dimer, ferritin), Troponin, NT-proBNP elevation
COVID-19 ➤ ARF

- **Exhaustion of anti-viral response**
  - ▼ IFN\(\gamma\) below detection levels
  - ▼ Natural Killer [secrete IFN\(\gamma\)]
  - ▼ CD4 Ag presenting cells

- **1/3 Macrophage Activation**
  - □ Driven by IL-1\(\beta\)
  - □ Ferritin > 4,420 ng/ml ➤ NF-\(\kappa\)B

- **2/3 Immune Dysregulation**
  - □ Driven by IL-6
  - □ HLA-DR mol. on CD14 < 5,000*
  - □ Ferritin < 4,420 ng/ml

* Tocilizumab restores HLA-DR on CD14 monocytes

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COVID-19 Macrophage Activation

- Diagnostic criteria
  - Ferritin level
  - H score

Severe COVID-19 Dysregulated SI

Laboratory markers

- **Inflammation**: ▲ ▲ TNF-α, IL-1β, and IL-6 …
  - similar to SARS, MERS, and non-viral ARDS
- **Acute phase response**: C-reactive protein, ferritin
- **Endothelial injury-Coagulation**: D-dimer, INR, platelet count

Clinical outcome

- ARF *similar* to ARDS ► MV - leading cause of death

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Dysregulated SI ➤ Role of CST

- The dysregulated *inflammation-coagulation* observed in COVID-19\(^1\) is qualitatively similar to multifactorial ARDS\(^2\)

- In non-viral ARDS: Strong clinical and experimental evidence ➤ prolonged CST effectively *downregulates* systemic and pulmonary inflammation-coagulation-fibroproliferation and accelerates resolution of ARDS \(^2,^3\)

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Compatible with CST-responsive disease

- **Computed tomography**¹
  - ground glass opacities

- **Histological findings**²,³
  - hyaline membrane
  - endothelial injury
    - lymphocytic interstitial infiltration
  - intra-alveolar fibrin balls –
  - intra-alveolar and bronchiolar cellular fibro-myxoid exudates
    - small /medium arteries cyt. vacuolization

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Corticosteroid Treatment

1. **Non-viral ARDS**: 10 RCTs ➤ Evidence of safety & efficacy
2. **Viral pneumonia**: WHO guidelines ▲ incomplete evidence
3. **Viral pneumonia**: large datasets adjusted for confounders with analysis based on timing, dose, and duration of CST
4. **COVID-19 pneumonia** - CST: promising early results
5. **COVID-19 pneumonia** - CST: guidelines: China, Korea, Italy
1. Non-viral ARDS: CST

- **Data Source**
- **Overall Response: Effectiveness & Safety**
  - Infl. markers; PaO$_2$:FiO$_2$; duration MV & ICU stay
  - Hospital mortality
  - Mechanical ventilation and ICU – free days to d 28
  - Complications: infectious and non-infectious
- **Treatment Protocol**
  - GC type, timing, duration*, mode of administration
  - Prophylaxis: nos. infections & glycemic variability

* includes tapering
ARDS GC Rx: Randomized CTs

No. of RCTs
N=10

- Methylprednisolone: 4
- Hydrocortisone *: 1
- Dexamethasone: 5

* HC + fludrocortisone = 1 RCT

No. of patients
N=1093

- Methylprednisolone: 494
- Hydrocortisone *: 277
- Dexamethasone: 322

* HC + fludrocortisone = 177 pts

References:
- Intensive Care Med 2016; 42: 829
- Lancet Respir Med vol 3; 267-276, 2020

Prolonged glucocorticoid treatment is associated with improved ARDS outcomes: analysis of individual patients’ data from four randomized trials and trial-level meta-analysis of the updated literature.
<table>
<thead>
<tr>
<th>Study</th>
<th>Reduction in Systemic Inflammation</th>
<th>Improvement in PaO₂:FiO₂</th>
<th>Reduction in MV duration</th>
<th>Reduction in ICU LOS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Consistent Response 10 RCTs N = 1093</td>
<td>Percentage [reported] 100%</td>
<td>100%</td>
<td>30%</td>
<td>100%</td>
</tr>
<tr>
<td><strong>Methylprednisolone</strong> [n=322] - Duration of Rx: 14-32 days – ¾ tapering after ext.</td>
<td>Meduri, 1998</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td>Steinberg, 2006</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td>Meduri, 2007</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td>Rezk, 2013</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Hydrocortisone</strong> [n=494] - Duration of Rx: 7 days – no tapering</td>
<td>Confalonieri, 2005</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td>Annane, 2006</td>
<td>Yes</td>
<td>Yes</td>
<td>No*</td>
</tr>
<tr>
<td></td>
<td>Sabry, 2011</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td>Liu, 2012</td>
<td>NR</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td>Rezk, 2013</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td>Tongyoo, 2016</td>
<td>NR</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td><strong>Dexamethasone</strong> [n=277] Duration of Rx: 5 days [20mg] + 5 days [10mg]</td>
<td>Villar, 2019</td>
<td>NR</td>
<td>Yes</td>
<td>Yes</td>
</tr>
</tbody>
</table>

**YES** = statistically significant improvement  
* IPDMA = Individual Pt Data Meta-Analysis

NR = not reported
RCTs: MVFD and Duration of MV

**MV-free days**
- Methylprednisolone (n=322): 8.53 (4.3-12.7) days, P < 0.0001
- Hydrocortisone (n=494): 4 days, (0.04-7.9), P = 0.05
- Dexamethasone (n=277): 4.8 days, (2.57-7.0), P < 0.0001

**Duration of MV**
- Methylprednisolone (n=322): 12.9 days, Δ10.1, P < 0.001
- Dexamethasone (n=277): 14.2 days, Δ5.3, P < 0.001

Increase in MVFD to d 28: CST vs. placebo

Duration of MV: CST vs. placebo
RCTs ARDS–GC Rx: Hsp. Mortality

* Study design favored the placebo group
NNT: Early ARDS = 4.5; Late ARDS = 6.0

# NNT = 6.5 for 60-day mortality
RCTs ARDS–GC Rx: Hsp. Mortality

Number needed to save one life

<table>
<thead>
<tr>
<th></th>
<th>RR (95% CI)</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hydrocortisone</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Annane 2006</td>
<td>0.87 (0.71, 1.07)</td>
<td>25.86</td>
</tr>
<tr>
<td>Confalonieri 2005</td>
<td>0.08 (0.01, 1.35)</td>
<td>0.86</td>
</tr>
<tr>
<td>Liu 2012</td>
<td>0.33 (0.08, 1.31)</td>
<td>3.28</td>
</tr>
<tr>
<td>Sabry 2011</td>
<td>0.44 (0.10, 1.99)</td>
<td>2.73</td>
</tr>
<tr>
<td>Tongyoo 2016</td>
<td>0.93 (0.66, 1.32)</td>
<td>19.87</td>
</tr>
<tr>
<td><strong>Subtotal (I-squared = 34.6%, p = 0.191)</strong></td>
<td>0.80 (0.59, 1.11)</td>
<td>52.60</td>
</tr>
</tbody>
</table>

| **Methylprednisolone**|             |        |
| Meduri 2007           | 0.56 (0.30, 1.03) | 11.43  |
| Meduri 1998           | 0.23 (0.06, 0.92) | 3.19   |
| Rezk 2013             | 0.08 (0.00, 1.32) | 0.82   |
| Steinberg 2006        | 0.65 (0.37, 1.13) | 12.96  |
| **Subtotal (I-squared = 21.1%, p = 0.283)** | 0.51 (0.31, 0.83) | 28.40  |

| **Dexamethasone**     |             |        |
| Villar 2020           | 0.66 (0.45, 0.95) | 19.00  |
| **Subtotal (I-squared = .%, p = .)** | 0.66 (0.45, 0.95) | 19.00  |
| **Overall (I-squared = 44.4%, p = 0.063)** | 0.67 (0.52, 0.87) | 100.00 |

https://journals.lww.com/ccejournal/Fulltext/2020/04000/Rationale_for_Prolonged_Corticosteroid_Treatment.18.aspx

* 6.5 at 60-days
ARDS  ▶  Prolonged CST is safe

- No change in rate of NM weakness, GI bleeding, NIs
- Transient hyperglycemia* ◀ larger initial [day 1] bolus

- No evidence of increased risk for nosocomial infections  ▶

* Transient hyperglycemia does not impact outcome
Key Points: Which drug and to Rx

- Methylprednisolone [MP] vs. Hydrocortisone [HC]
  - Outcomes: MP superior to HC
  - Bolus: to achieve early greater GR saturation [max at MP 100 mg]
  - Infusion: steady state-prevents glycemic variability
  - Duration: approximately 24 days superior to 7 days

- Dexamethasone: once daily x 10 d ► very effective

- Tapering: MUST – Restart Rx if rebound: MUST

- Infections surveillance
  - important to identify nosocomial infections in absence of fever
**ARDS: Prolonged CST – Protocols**

**Methylprednisolone [mg]**
- **Day 0- Bolus**: 1 mg/kg
- **0 to 14**: 1 mg/kg
- **15 to 21**: 0.5 mg/kg
- **22 to 25**: 0.25 mg/kg
- **26 to 28**: 0.125 mg/kg

*If extubated before day 14 advance to day 15*

**Dexamethasone [mg]**
- **1 to 5**: 1 to 5 mg
- **6 to 10**: 6 to 10 mg
- **11 to 14**: 11 to 14 mg

*Optional Not in the Protocol*

*Slower tapering to minimize rebound inflammation*

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*Results of a Randomized Controlled Trial (CHEST 2007; 131:954-963)*

*Lancet Respir Med vol 3; 267-276, 2020*
**Methylprednisolone Rx Protocol**

- Protocol recommended by the 2017 SCCM and ESICM Task Force

Plasma IL-6 predictor of ARF

- COVID-19: Higher IL-6 levels in pts requiring ICU and MV
- Tocilizumab appears to be efficacious – What about CST?

**Figure 2. Meta-Analysis of Serum IL-6 Levels in COVID-19**

**Panel A. Patients with Complicated COVID-19 versus Non-Complicated**

<table>
<thead>
<tr>
<th>Study Subgroup</th>
<th>Log(Ratio of Means)</th>
<th>SE</th>
<th>Total</th>
<th>Weight</th>
<th>Ratio of Means</th>
<th>IV, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chen et al., 2020a</td>
<td>0.75930559</td>
<td>0.17793404</td>
<td>14</td>
<td>15</td>
<td>16.7%</td>
<td>2.12 (2.05, 2.18)</td>
</tr>
<tr>
<td>Dao et al., 2020</td>
<td>1.5808391</td>
<td>0.15758802</td>
<td>20</td>
<td>20</td>
<td>100.0%</td>
<td>3.46 (3.24, 3.68)</td>
</tr>
<tr>
<td>Huang et al., 2020a</td>
<td>1.03469647</td>
<td>0.08732466</td>
<td>13</td>
<td>28</td>
<td>16.6%</td>
<td>2.31 (2.27, 2.35)</td>
</tr>
<tr>
<td>Liu 2020</td>
<td>2.93826309</td>
<td>0.09354648</td>
<td>9</td>
<td>11</td>
<td>10.0%</td>
<td>4.17 (4.05, 4.30)</td>
</tr>
<tr>
<td>Qi et al., 2020</td>
<td>0.42273705</td>
<td>0.07036103</td>
<td>286</td>
<td>286</td>
<td>100.0%</td>
<td>3.97 (3.91, 4.03)</td>
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<tr>
<td>Wu et al., 2020</td>
<td>0.23409484</td>
<td>0.03386244</td>
<td>84</td>
<td>117</td>
<td>15.7%</td>
<td>2.23 (2.12, 2.34)</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td></td>
<td></td>
<td>486</td>
<td>616</td>
<td>100.0%</td>
<td>2.90 (2.17, 3.91)</td>
</tr>
</tbody>
</table>

**Panel B. Patients Requiring ICU Admission versus Not Requiring ICU Admission**

<table>
<thead>
<tr>
<th>Study Subgroup</th>
<th>Log(Ratio of Means)</th>
<th>SE</th>
<th>Total</th>
<th>Weight</th>
<th>Ratio of Means</th>
<th>IV, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chen et al., 2020a</td>
<td>1.0861089</td>
<td>0.03533802</td>
<td>20</td>
<td>479</td>
<td>59.9%</td>
<td>3.62 (3.53, 3.74)</td>
</tr>
<tr>
<td>Huang et al., 2020a</td>
<td>1.03469647</td>
<td>0.08732466</td>
<td>13</td>
<td>28</td>
<td>16.6%</td>
<td>2.31 (2.27, 2.35)</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td></td>
<td></td>
<td>486</td>
<td>507</td>
<td>100.0%</td>
<td>3.24 (2.54, 4.14)</td>
</tr>
</tbody>
</table>

Interleukin-6 in COVID-19: A Systematic Review and Meta-Analysis

https://doi.org/10.1101/2020.03.30.20048058

Level of IL-6 predicts respiratory failure in hospitalized symptomatic COVID-19 patients

https://doi.org/10.1101/2020.04.01.20047381
CST- Effective in ▼▼ IL-6 levels

- Three studies (2 RCTs) ➤ methylprednisolone = effective in decreasing plasma$^{1,2}$ and BAL$^{3}$ IL-6 levels, and much more ...

- Early ARDS

- Late ARDS

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Corticosteroid Treatment

1. Non-viral ARDS: 10 RCTs ▶ Evidence of safety & efficacy

2. COVID-19 pneumonia: WHO guidelines ◀ incomplete evidence

3. Viral pneumonia: large datasets adjusted for confounders with analysis based on timing, dose, and duration of CST

4. COVID-19 pneumonia - CST: promising early results

5. COVID-19 pneumonia - CST: guidelines: China, Korea, Italy

6. COVID-19 pneumonia - CST: EB Recommendations
2. WHO guidelines ◀ incomplete evidence

The WHO based on “Given the lack of effectiveness and possible harm” … made the decision “of not recommending the routine use of corticosteroids for treatment of viral pneumonia outside clinical trials”

The evidence for lack of effectiveness was based on the findings of 4 publications

1. 2006 outdated and poor-quality meta-analysis
2. 2016 meta-analysis limited to 10 observational studies (< 1500 patients) most without reporting indications for CST details on timing, dose, and duration.
3. Two retrospective observational studies without a pre-designed study protocol involving 600 patients with H1N1 and 300 patients with MERS pneumonia
   - After adjustment for (i) baseline imbalances, (ii) post-baseline time-dependent pt. differences that influence the decision to prescribe CST > no mortality benefits
   - MERS study: CST duration affected viral clearance: < 7 days = increased; > 7 days no impact! [detailed not mention in WHO document]


That’s IT

It is unlikely that delayed viral clearance would have a greater negative impact on outcome than the host own “cytokine storm”.

2. Lancet Letters ➤ incomplete evidence


Corticosteroid Treatment

1. **Non-viral ARDS:** 10 RCTs ➤ Evidence of safety & efficacy

2. **COVID-19 pneumonia:** WHO guidelines ◀ incomplete evidence

3. **Viral pneumonia:** 4 large datasets adjusted for confounders with analysis based on timing, dose, and duration of CST

4. **COVID-19 pneumonia - CST:** promising early results

5. **COVID-19 pneumonia - CST:** guidelines: China, Korea, Italy

6. **COVID-19 pneumonia - CST:** EB Recommendations
3. CST-SARS pneumonia: 2 large studies

- Two large studies \( n=401,1280 \): overall no reduction in mortality
  - Subgroup analyses showed benefits
  - Effective in critical SARS cases
    - MP better than HC

Results: Among the 401 SARS patients studied, 147 of 249 noncritical patients (59.0%) received corticosteroids (mean daily dose, 105.3 ± 86.1 mg [± SD]), and all survived the disease; 121 of 152 critical patients (79.0%) received corticosteroids at a mean daily dose of 133.5 ± 102.3 mg, and 25 died. Analysis of these 401 confirmed cases did not show any benefit of corticosteroid on the death rate and hospitalization days. However, when focused on 152 critical SARS cases, factors correlated with these end points indicated by univariate analysis included use of corticosteroid, age, rigor at onset, secondary respiratory infections, pulmonary rales, grading of OI, and use of invasive ventilation. After adjustment for possible confounders, treatment with corticosteroid was shown contributing to lower overall mortality, instant mortality, and shorter hospitalization stay (\( p < 0.05 \)). Incidence of complications was significantly associated with the need for invasive ventilation but not with use of corticosteroids.

Corticosteroid treatment of severe acute respiratory syndrome in Hong Kong

*The Guangzhou Experience* (CHEST 2006; 129:1441-1452)

The present study is the largest comprehensive review to date of the use of corticosteroids in SARS treatment. On multivariate analysis, corticosteroid use as a whole did not show survival benefit compared with no steroid use. However, when individual corticosteroid types were analysed, Group MP (intravenous methylprednisolone) conferred lower mortality compared with Group No Steroid, which is statistically significant. Among the corticosteroid groups, Group MP and Group P (oral prednisolone) showed similar survival outcome.
3. CST-viral pneumonia: largest datasets

- Two largest studies\(^1,2\) evaluated impact of time, dose, and duration of CST> significant reduction in mortality with protocol \(\cong\) to one recommended by SCCM and ESICM TF.\(^3\)

- SARS study; n= 5327 patients - after adjustment for possible confounders, CST was safe and decreased the risk for death by 47% (HR 0.53, 95% CI: 0.35-0.82) \(^1\) - best results with MP 80mg/d

- H1N1 study; n = 2141 patients - subgroup analysis among pts. with PaO\(_2/\text{FiO}_2\) <300 mm Hg (535 vs. 462), low-to-moderate-dose CST significantly reduced both 30-day mortality (aHR 0.49 [95% CI 0.32-0.77]) and 60-day mortality (aHR 0.51 [95% CI 0.33-0.78])

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4. CST-SARS: largest dataset \( n = 5327 \)

- CST decreased mortality by 47% in severe cases
- Most effective protocol \( \cong \) to one recommended by SCCM and ESICM TF

Multivariate Cox regression analysis

With adjustment for gender, age, occupation, mechanical ventilation, severity of cases, complications (MODS, DM, infection, DIC etc.), and primary diseases (hypertension, cardiovascular and cerebrovascular diseases, cancer, renal failure/chronic renal disease etc.), multivariate Cox’s proportional hazard regression showed that usage of GC prolonged survival period of clinical cases significantly (\( P=0.03 \)) and death risk dropped by 63% (HR: 0.37, 95% CI: 0.24-0.56) and 43% (HR: 0.57, 95% CI: 0.37-0.86) for average daily doses of 0-80 mg/d and 80-160 mg/d, respectively. Starting doses, mean doses in first three days, daily maximum doses, and accumulated doses did not show significant differences.

Definition of severe SARS – any of 4: tachypnea (>20 bpm); \( \text{PaO}_2 \) < 70 mmHg; \( \text{O}_2 \) sat < 92%; sternum score >2

4. CST-H1N1: largest dataset $n = 2141$

- Pts with $P/F < 300$: moderate CST reduced 30-day mortality (aHR 0.49 [95% CI 0.32-0.77]); high-dose CST yielded no difference.

All pts [$n=530$]

- $6.8\%$ vs. $14.7\%$

$P/F < 300$ [$n=351$]

- $8.1\%$ vs. $20.2\%$

$P/F > 300$ [$n=179$]

- $4.3\%$ vs. $3.4\%$

**FIGURE 2** Kaplan-Meier survival curves for matched patients treated with low-to-moderate-dose corticosteroids or with no corticosteroids

Corticosteroid Treatment

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CST-COVID-19: early promising results

- Single center - Wuhan, China - 201 pts
- IL-6 correlated with mortality
- Sicker pts. ➤ MP protocol recommended by the 2017 SCCM and ESICM TF ¹
- 84 developed ARDS
  - MP Rx [n=50]: mortality 46%
  - No MP Rx [n=34]: mortality 62%
  - HR 0.38; 95% CI 0.20-0.72, p=0.003
- MP Rx may benefit pts with ARDS
- ?premature discontinuation [see fig]

CST-COVID-19: early promising results

- 91 COVID-19 pts: including 26 severe
- 22 pts Rx with MP boluses [40-500mg]
  - Rapid improvement in PaO2...
  - 1 of 22 ➤ ETI/ MV
- Safe
- Conclusion

- No impact on neg. conversion

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- Time from positive to negative conversion
  SARS-CoV-2-nucleic acid in nasopharyngeal swabs

- No impact on neg. conversion

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https://doi.org/10.1101/2020.04.06.20054890
CST-COVID-19: early promising results

- 46 pts - 26 pts Rx with MP
- MP Rx 1-2mg/Kg x 7 days – duration adjusted to reduction in inflammatory markers
- Improved CT resolution and O2 saturation
- Safe

Figure 3 Images of chest CT scan on day 1, 7 and 14 after hospitalization in severe COVID-19 pneumonia patients with and without methylprednisolone treatment

medRxiv preprint doi: https://doi.org/10.1101/2020.03.06.20032342.
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6. **COVID-19 pneumonia - CST:** EB Recommendations
5. National Recommendations

- **China**
  - On the use of corticosteroids for 2019-nCoV pneumonia
  - Lianhan Shang, Jianping Zhao, Yi Hu, Ronghui Du, Bin Cao

- **Italy**
  - National Institute for the Infectious Diseases
  - "L. Spallanzani", IRCCS.
  - Recommendations for COVID-19 clinical management
  - Emanuele Narditi, Nicola Petrosillo, Tommaso Aversa Bartella, Luca Luongo, Andrew Mood, Federico Palmieri, Giampaolo O'Ortelli, Laura Murchioni, Silvia Marchetti, Giuseppe Ippolito, Andrea Antinori for the INMI COVID-19 Treatment Group (ICOTREG)
  - National Institute for Infectious Diseases
  - "L. Spallanzani", IRCCS, Rome, Italy

**Supportive therapy:**
- O₂ administration
- Aantimicrobial therapy (broad spectrum-empiric or based on microbiological results)
- Oral or intravenous rehydration
- Consider systemic steroids administration in case of clinical signs suggesting an incipient worsening of respiratory functions (steroids are mandatory if Tocilizumab is used) (methylprednisolone 1 mg/Kg daily intravenously for 5 days, followed by 40 mg daily for 3 days and, lastly, 10 mg daily for 2 days, or dexamethasone 20 mg daily intravenously for 5 days, followed by 10 mg daily for 3 days and lastly 5 mg daily for 2 days)
Corticosteroid Treatment

1. **Non-viral ARDS**: 10 RCTs ➤ Evidence of safety & efficacy
2. **COVID-19 pneumonia**: WHO guidelines ▼ incomplete evidence
3. **Viral pneumonia**: large datasets adjusted for confounders with analysis based on timing, dose, and duration of CST
4. **COVID-19 pneumonia - CST**: promising early results
5. **COVID-19 pneumonia - CST**: guidelines: China, Korea, Italy
6. **COVID-19 pneumonia - CST**: EB Recommendations
6. Is CST Effective? ▶ Evidence

- **Non-viral ARDS** - 10 RCTs [n=1093] - Safe and sizable ▼▼ in duration of MV, ICU LOS, and mortality

- **Viral pneumonia** – SARS – H1N1: 4 large datasets*
  - **SARS** [n = 7008 (401+1280+5327)] - Safe and ▼▼ mortality in severe SARS
  - best response: methylpred. 80 mg QD – duration weeks
  - **H1N1** [n = 2141] - Safe and ▼▼ mortality in those with PaO₂:FiO₂ < 300
  - **COVID-19** limited but encouraging data
    - improved oxygenation, CT resolution, ▼▼ mortality

* Analysis include adjustments for confounders and evaluation of CST components
6. Recommended intervention

- MP dose adjusted to IBW – usual initial dose 80 mg is OK
- Monitor daily PaO$_2$:FiO$_2$, CRP, D-dimer, ferritin, PCT, ...
- If no response or worsening, consider doubling the dose

- Recommend co-intervention to correct hypovitaminosis
  - Vitamin C 1.5 g Q 6 h [100 cc NS] / 4 days *
  - Thiamine 100 mg Q 12 h [100 cc D5W] / 4 days
  - Vitamin D 480,000 IU dose (60ml) / 1 day
  - Recheck vit D level on day 5. If low, supplement 96,000 IU / day for 5 days

- On MV for >7 days ► infection surveillance with NB-BAL
- Elevated PCT ► infection w/u – empiric ATB

MP= methylprednisolone * Alternative Vit C [P. Marik] 3 g Q6 hours for seven days
Early Intervention ➤ Prevent MV

- **Entry Criteria**: Pneumonia + P/F < 250 + CRP > 100 mg/L
- **Day 1**: MP 80mg bolus, … followed by
- **Continuous infusion**: MP 80mg for [1] > 8 days \(\text{AND} \) [2] P/F > 350 OR CRP \(\leq\) 20 mg/L
- **Switch to oral**: MP 16mg BID* UNTIL [1] CPR < 20% normal OR [2] P/F > 400 OR O2 sat \(\geq\) 95% on RA … followed by
- **Slow taper**: over 6 days [16 mg QD x 3 d, QD x 3 d]

* Prof. Marco Confalonieri - Trieste Italy

* If NPO > or MP 20mg IV BID

NCT04323592*
Early Rx intervention: shorter guided duration

- **Criteria A**
  - PaO2/FiO2 > 350 or
  - CRP < 20mg/L

- **Criteria B**
  - PaO2/FiO2 > 400* or
  - CRP < 20% normal

* or SatHbO2 ≥ 95% on ambient air

* Prof. Marco Confalonieri - Trieste Italy
COVID-19 on Mechanical Ventilation

Both interventions are highly effective

- Methylprednisolone [mg]
  - Day 0- Bolus: 1 mg/kg
  - Day 0 to 14: 1 mg/kg
  - Day 15 to 21: 0.5 mg/kg
  - Day 22 to 25: 0.25 mg/kg
  - Day 26 to 28: 0.125 mg/kg

  If extubated before day 14, advance to day 15

- Dexamethasone [mg]
  - Day 1 to 5: 1 to 5 mg
  - Day 6 to 10: 6 to 10 mg
  - Day 11 to 14: 11 to 14 mg

*slower tapering to minimize rebound inflammation

Optional
Not in the Protocol


Haemophagocytic lymphohistiocytosis (HLH)

- CTL* fail to eliminate Ag presenting activated macrophages
- Activated macrophages [downregulation] → Cytokine storm
  - ▲▲ TNF-α, IL-1β, IL-6, IL-8, IL-10 …..
- Laboratory findings:
  - ▲▲ serum ferritin [5,000 - >10,000], CRP
  - ▲ LFT: AST, ALT, LDH, bil., triglycerides
  - ▲ D-dimer — ▲ INR, ▼ platelet count, ▼ Hb
- Sudden and rapid deterioration in MODS

*CTL = Cytotoxic lymphocytes that lyse macrophages bearing foreign antigen

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COVID-19 HLH-like syndrome

Treatment

- High dose methylpred.: 120 mg Q 8 h > 3 days
  - wean base on ferritin CRP, IL-6, etc.
  - return to 1mg/kg ► follow ARDS protocol
- Tocilizumab (IL-6 inhibitor) per guidelines
- Consider plasma exchange

Rafael L.B. Yes, yes, yes

We floundered for two weeks. Lots of codes, intubations and death. Maybe 15 discharges.

We started steroids and discharge 250 patients. Less intubations, less codes. And the ones that ended up on vent, not as serious.

CXR/CT Changes = steroids
Hypoxia on admission = steroids
Ambulatory hypoxia = steroids
Completely changed our trajectory

Steroids are a game changer

Hospitalist, SE Michigan - our group is taking care of 700 plus COVID+ patients

John DP

I’m here in New Orleans and we’ve been using it for the last four weeks. We notice a great success once we started using steroids.

Do not underestimate this study. This was a game changer in our hospital. We were able to free ventilators and get elderly patient out of the hospital without needing a ventilator.

Patients that were obviously crushing quickly, who we had to have end of life talk with were able to walk out of the hospital. At no point did any of our patient worsen and because of steroids.

These patients shed viruses 4 weeks later, With or without steroids. The virus doesn’t kill anybody, it’s the inflammation that does.

Let the virus replicate however slow down the inflammation
**Rationale for Prolonged Corticosteroid Treatment in the Acute Respiratory Distress Syndrome Caused by Coronavirus Disease 2019**

Jesús Villar, MD, PhD; Marco Confalonieri, MD; Stephen M. Pastores, MD, MACP, FCCP, FCCM; G. Umberto Meduri, MD

[https://journals.lww.com/ccejournal/Fulltext/2020/04000/Rationale_for_Prolonged_Corticosteroid_Treatment.18.aspx](https://journals.lww.com/ccejournal/Fulltext/2020/04000/Rationale_for_Prolonged_Corticosteroid_Treatment.18.aspx)

**Michigan and New Orleans Front-line**

“Steroids are a game changer”