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

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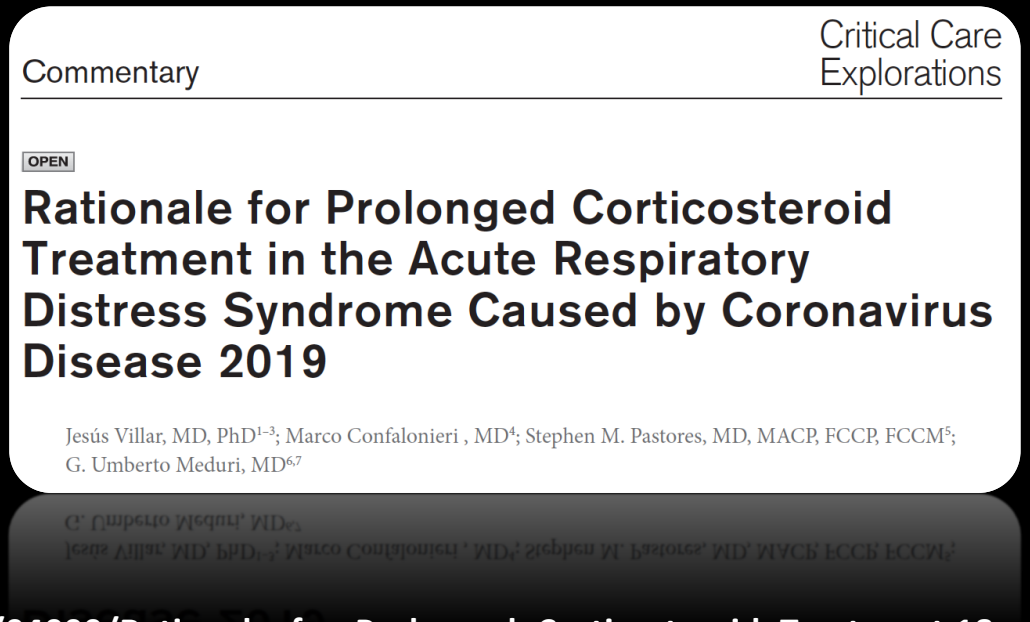
https://journals.lww.com/ccejournal/Fulltext/2020/04000/Rationale_for_Prolonged_Corticosteroid_Treatment.18.aspx

Disclosure - Conflict of Interest

- ❑ None
- ❑ Academic Bias



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

Academic Freedom Saves Lives *DOI: 10.13140/RG.2.1.3936.1762*

COVID-19 A National Emergency

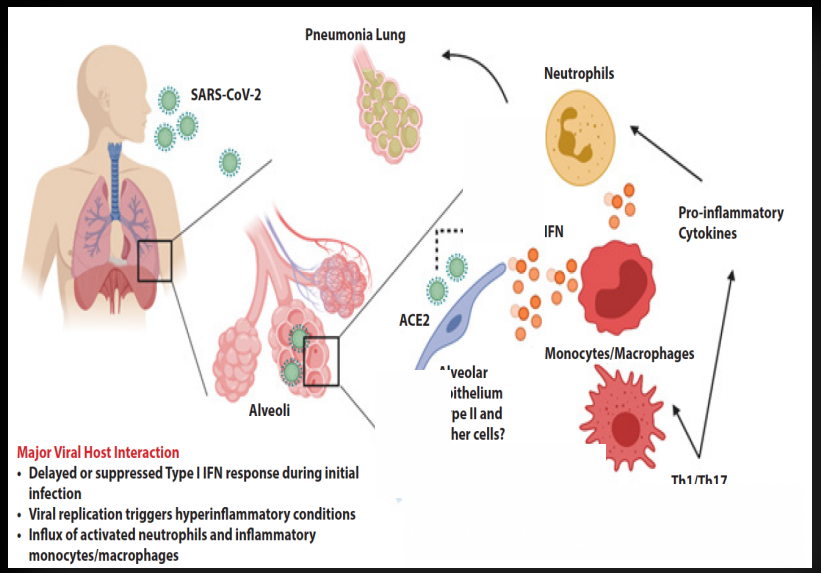
- USA TODAY – March 18, 2020 "***Too many coronavirus patients, too few ventilators: Outlook in US could get bad, quickly*** *… As we face potentially 'the largest workforce crisis in our generation,' hospitals are bracing for ventilator shortages amid the coronavirus outbreak.*" [1]

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

1. https://www.usatoday.com/story/news/health/2020/03/18/coronavirus-ventilators-us-hospitals-johns-hopkins-mayo-clinic/5032523002/

Immunology COVID-19: simplified

❑ Suppressed anti-viral defense and amplified inflammation



Aerosolized uptake of SARS-CoV-2 leads to infection of ACE2 expressing target cells such as alveolar type 2 cells or other unknown target cells. Virus may dampen anti-viral IFN responses resulting in uncontrolled viral replication. The influx of neutrophils and monocytes/macrophages results in hyperproduction of pro-inflammatory cytokines. The immunopathology of lung may be the result of the "cytokine storms". Specific Th1/Th17 may be activated and contributes to exacerbate inflammatory responses. B cells/plasma

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

Optimal response

Dysregulated response

Suppressed
▲Viral replication

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

Apoptosis B and T cells

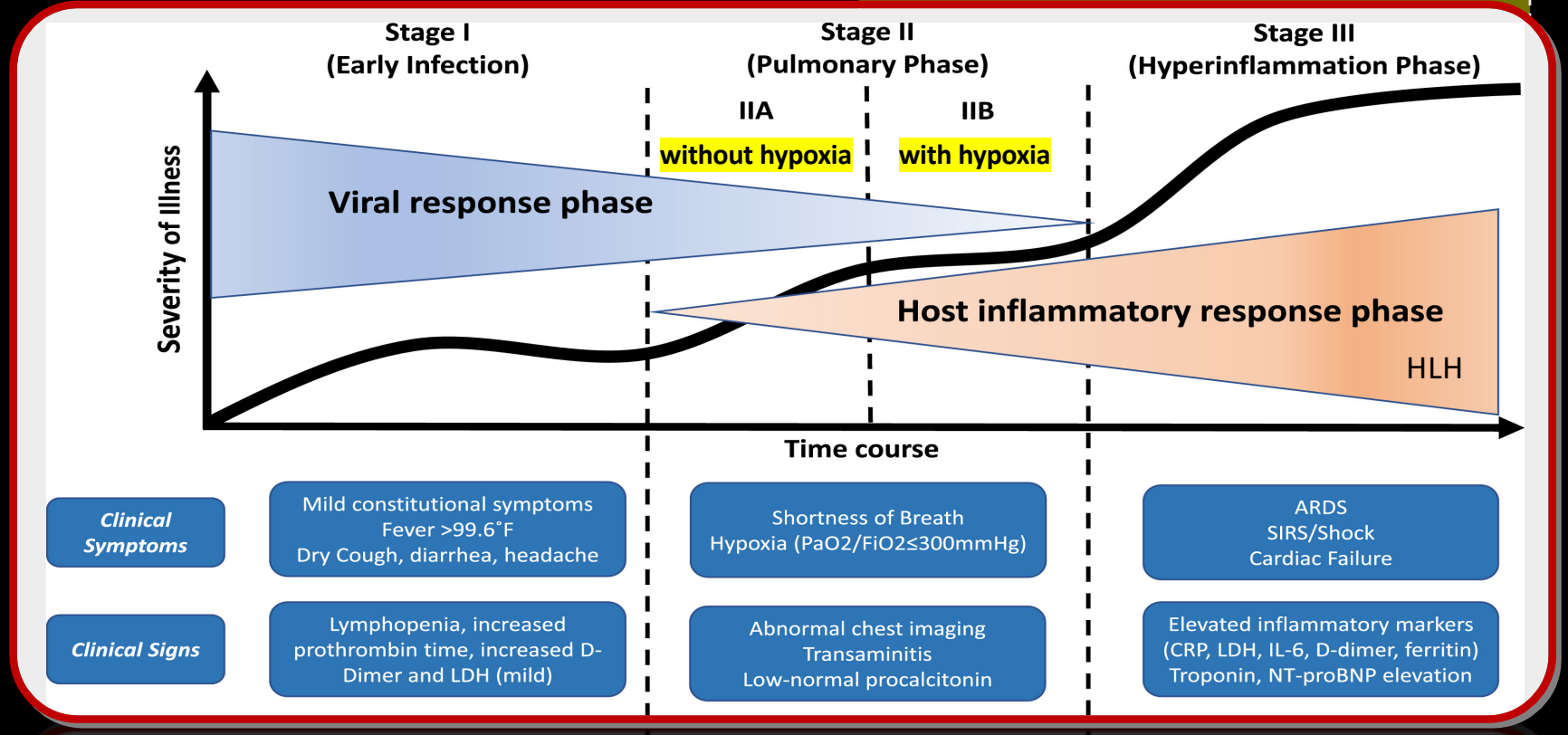
Amplified

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

Prompetchara E, at al.: **Immune responses in COVID-19 and potential vaccines: Lessons learned from SARS and MERS epidemic**. *Asian Pac J Allergy Immunol* 2020, **38**(1):1-9.

- exhausted anti-viral defense
- dysregulated inflammation



The Journal of Heart and Lung Transplantation

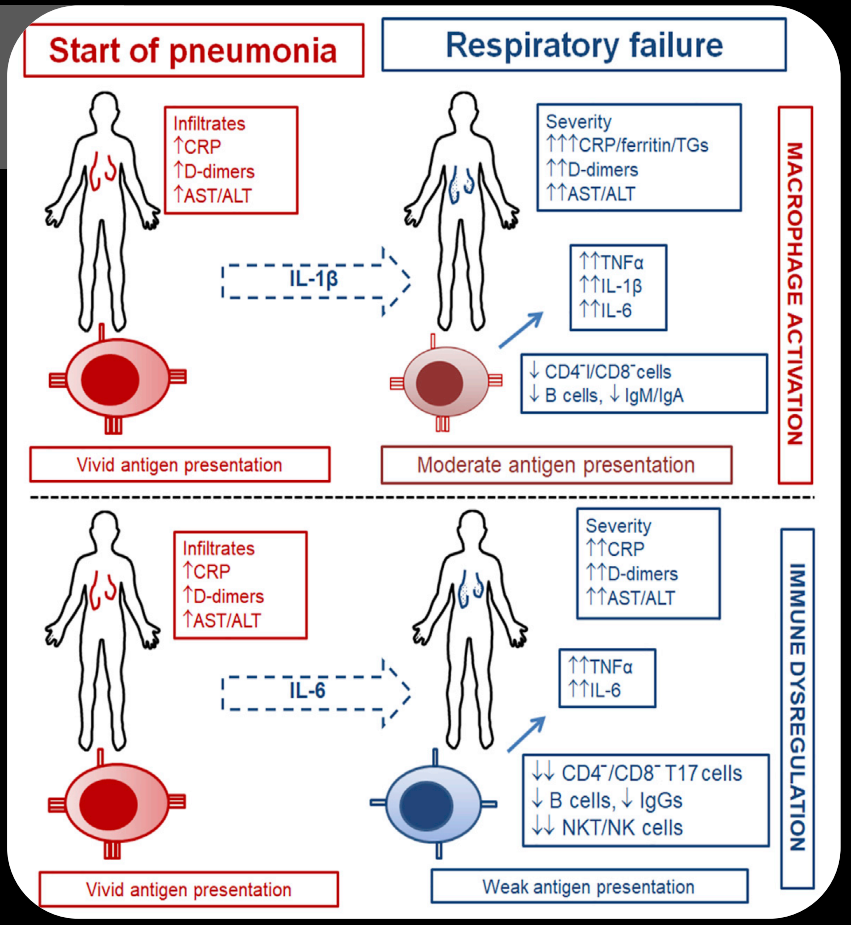
COVID-19 Illness in Native and Immunosuppressed States: A Clinical-Therapeutic Staging Proposal

COVID-19 ►ARF

▼ lymphocytes

- ❑ **Exhaustion of anti-viral response**
  - ❑ ▼ IFNγ below detection levels
  - ❑ ▼ Natural Killer [secrete IFNγ]
  - ❑ ▼ CD4 Ag presenting cells
- ❑ 1/3 **Macrophage Activation**
  - ❑ Driven by IL-1β
  - ❑ Ferritin > 4,420 ng/ml ► NF-kB
- ❑ 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

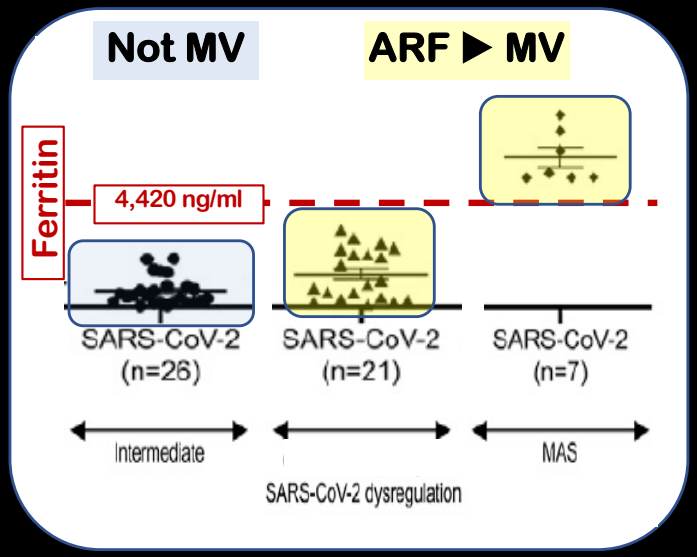


Giamarellos-Bourboulis *et al*: **Complex Immune Dysregulation in COVID-19 Patients with Severe Respiratory Failure**. *Cell Host Microbe* 2020.

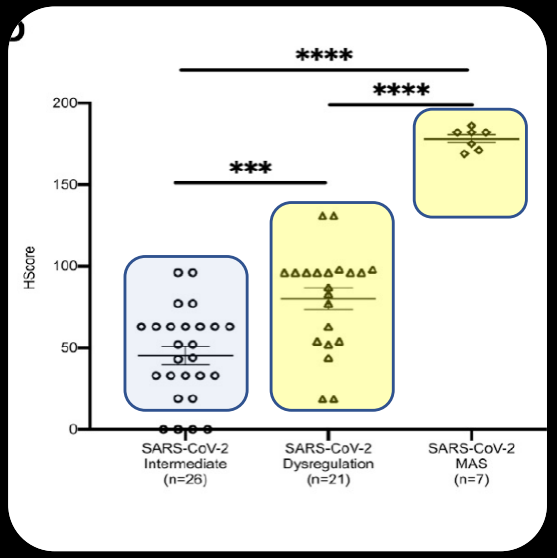
COVID-19 Macrophage Activation

❑ Diagnostic criteria

❑ Ferritin level



❑ H score



HS score>150 [optional]

	Numbero
Temperature	
<38·4°C	0
38·4–39·4°C	33
>39·4°C	49
Organomegaly	
None	0
Hepatomegaly or splenomegaly	23
Hepatomegaly and splenomegaly	38
Number of cytopenias*	
One lineage	0
Two lineages	24
Three lineages	34
Triglycerides (mmol/L)	
<1·5 mmol/L	0
1·5–4·0 mmol/L	44
>4·0 mmol/L	64
Fibrinogen (g/L)	
>2·5 g/L	0
≤2·5 g/L	30
Ferritin ng/ml	
<2000 ng/ml	0
2000–6000 ng/ml	35
>6000 ng/ml	50
Serum aspartate aminotransferase	
<30 IU/L	0
≥30 IU/L	19
Haemophagocytosis on bone marrow aspirate	
[redacted]	
Known immunosuppression†	
No	0
Yes	18

Giamarellos-Bourboulis *et al.* **Complex Immune Dysregulation in COVID-19 Patients with Severe Respiratory Failure.** *Cell Host Microbe* 2020.

Severe COVID-19 Dysregulated SI

Laboratory markers [1]

- ❑ **Inflammation**: ▲ ▲ TNF-α, IL-1β, and **IL-6** …
  - ➢ similar to SARS, [2] MERS, [2] and non-viral ARDS [3]
- ❑ **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

1. Henry BM et al. **Hematologic, biochemical a- immune biomarker abnormalities in COVID-19 meta-analysis**. *Clinical Chem and Lab MediCCLM)* 2020 (on line)
2. Qin C, Zhou L, Hu Z, et al. Dysregulation of immune response in patients with COVID-19 in Wuhan, China. *Clin Infect Dis.* 2020
3. Meduri GU et al. Activation and regulation of systemic inflammation in ARDS: Rationale for prolonged glucocorticoid therapy. *Chest.* 2009;136:1631-43

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]

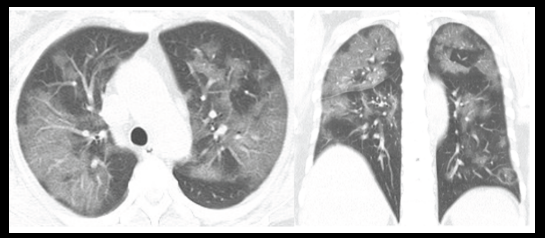
1. Qin C, Zhou L, Hu Z, et al. Dysregulation of immune response in patients with COVID-19 in Wuhan, China. *Clin Infect Dis.* 2020
2. Meduri GU et al. Activation and regulation of systemic inflammation in ARDS: Rationale for prolonged glucocorticoid therapy. *Chest.* 2009;136:1631-43
3. Annane D, et al. Guidelines for the Diagnosis and Management of Critical Illness-Related Corticosteroid Insufficiency (CIRCI) in Critically Ill Patients (Part I): Society of Critical Care Medicine (SCCM) and European Society of Intensive Care Medicine (ESICM) 2017. *Critical Care Medicine.* 2017;45(12):2078-2088.

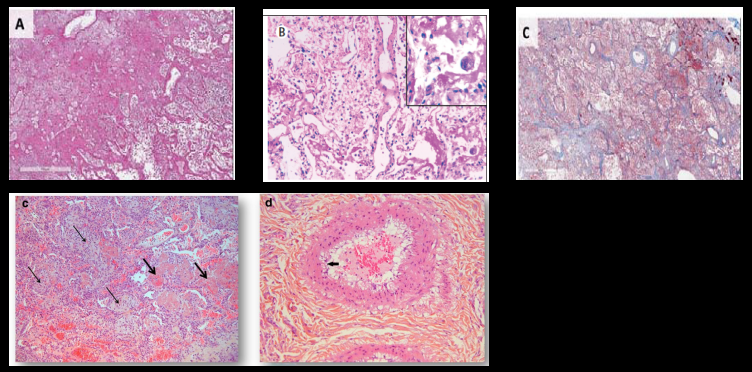
Compatible with CST-responsive disease

- ❑ **Computed tomography**[1]
  - ✓ ground glass opacities
- ❑ **Histological findings** [2,3]

Early phase
- ✓ hyaline membrane
- ✓ endothelial injury
- ✓ lymphocytic interstitial infiltration

Late phase
- ✓ intra-alveolar fibrin balls –
- ✓ intra-alveolar and bronchiolar cellular fibro-myxoid exudates
- ✓ small /medium arteries cyt. vacuolization





1. Tang L et al. Severe COVID-19 Pneumonia: Assessing Inflammation Burden with Volume-rendered Chest CT. *Radiology: Cardiothoracic Imaging.* 2020;2(2):e200044.
2. Xu Z et al. Pathological findings of COVID-19 associated with acute respiratory distress syndrome. *The Lancet Respiratory Medicine.* 2020.
3. Copin MC et al. Time to consider histologic pattern of lung injury to treat critically ill patients with COVID-19 infection/ Intensive Care Medicine 2020 https://doi.org/10.1007/s00134-020-06057-8

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
6. **COVID-19 pneumonia** - CST: EB Recommendations

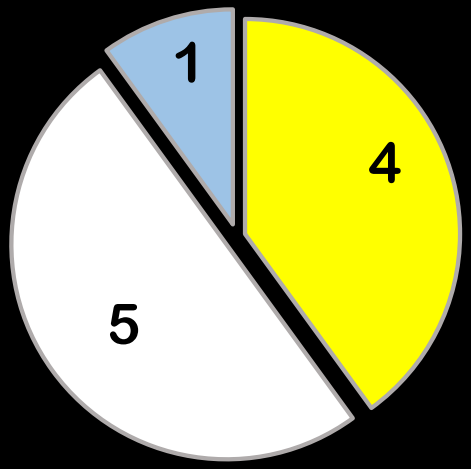
1. Non-viral ARDS: CST

- ❑ **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



- Methylprednsolone
- Hydrocortisone *
- Dexamethasone

* HC + fludrocortisone = 1 RCT

No. of patients N=1093

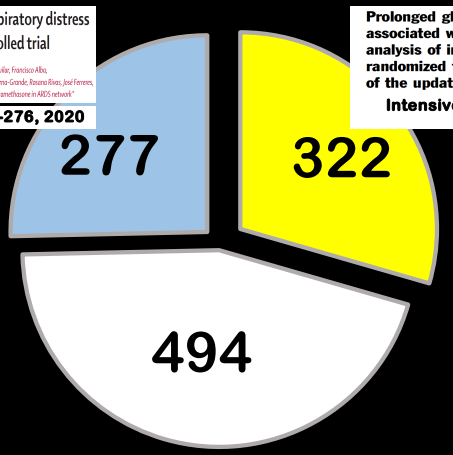
Dexamethasone treatment for the acute respiratory distress syndrome: a multicentre, randomised controlled trial

Jesús Villar, Carlos Fernando, Domingo Martínez, Alfonso Ambrós, Tomás Muñoz, Juan A Soler, Gerardo Aguilar, Francisco Alba, Elena González-Higueras, Luis A Canova, Carmen Martín-Rodríguez, Francisco J Baez-Dominguez, Pablo Serna-Grande, Rosana Rivas, José Ferreres, Javier Bobda, Lucía Capilla, Alex Tallet, José M Añón, Rosa L Fernández, Jesús M González-Martín for the dexamethasone in ARDS network*

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

Intensive Care Med 2016; 42: 829



- Methylprednsolone
- Hydrocortisone *
- Dexamethasone

* HC + fludrocortisone = 177 pts

Consistent Response

32 YES
6 NR
2 No

NR = not reported

Study 10 RCTs N = 1093	Reduction in Systemic Inflammation	Improvement in PaO_2:FiO_2	Reduction in MV duration	Reduction in ICU LOS
Percentage [reported]	100%	100%	80%	100%
Methylprednisolone [n=322] - Duration of Rx: 14-32 days – ¾ tapering after ext.				
Meduri,1998	Yes	Yes	Yes	Yes
Steinberg, 2006	Yes	Yes	Yes	Yes
Meduri, 2007	Yes	Yes	Yes	Yes
Rezk, 2013	Yes	Yes	Yes	Yes
Hydrocortisone [n=494] - Duration of Rx: 7 days – no tapering				
Confalonieri, 2005	Yes	Yes	Yes	Yes
Annane, 2006	Yes	Yes	*No**	*NR*
Sabry, 2011	Yes	Yes	Yes	*NR*
Liu, 2012	*NR*	Yes	Yes	Yes
Rezk, 2013	Yes	Yes	Yes	Yes
Tongyoo, 2016	*NR*	Yes	*No*	*NR*
Dexamethasone [n=277] Duration of Rx: 5 days [20mg] + 5 days [10mg]				
Villar, 2019	*NR*	Yes	Yes	Yes

I P D M A*

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

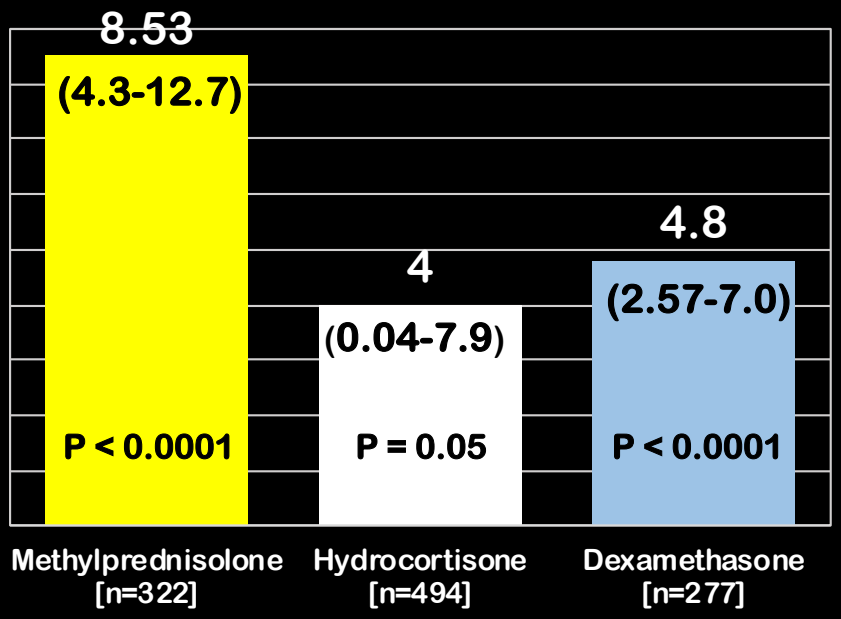
Intensive Care Med 2016; 42: 829

YES = statistically significant improvement

* IPDMA = Individual Pt Data Meta-Analysis

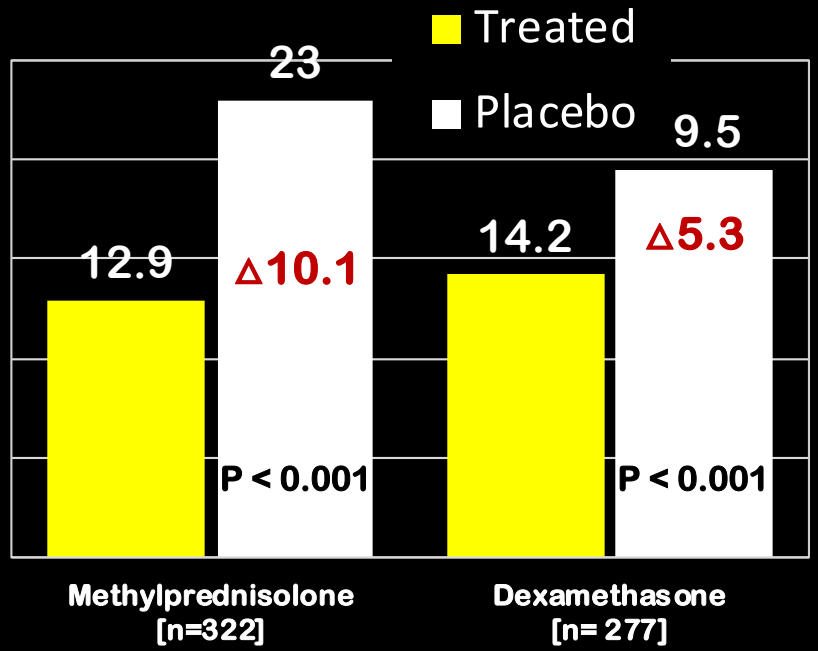
RCTs: MVFD and Duration of MV

❑ Δ MV-free days



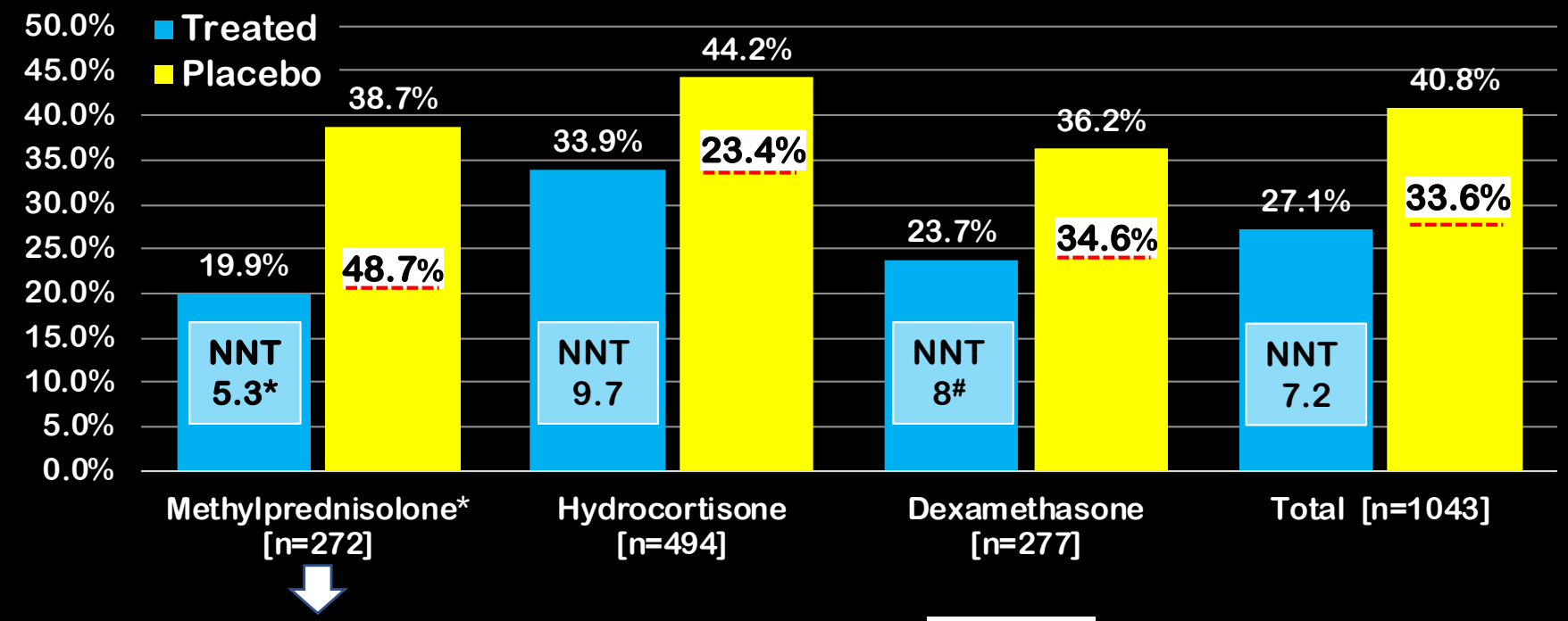
Increase in MVFD to d 28: CST vs. placebo

❑ Duration of MV



Duration of MV: CST vs. placebo

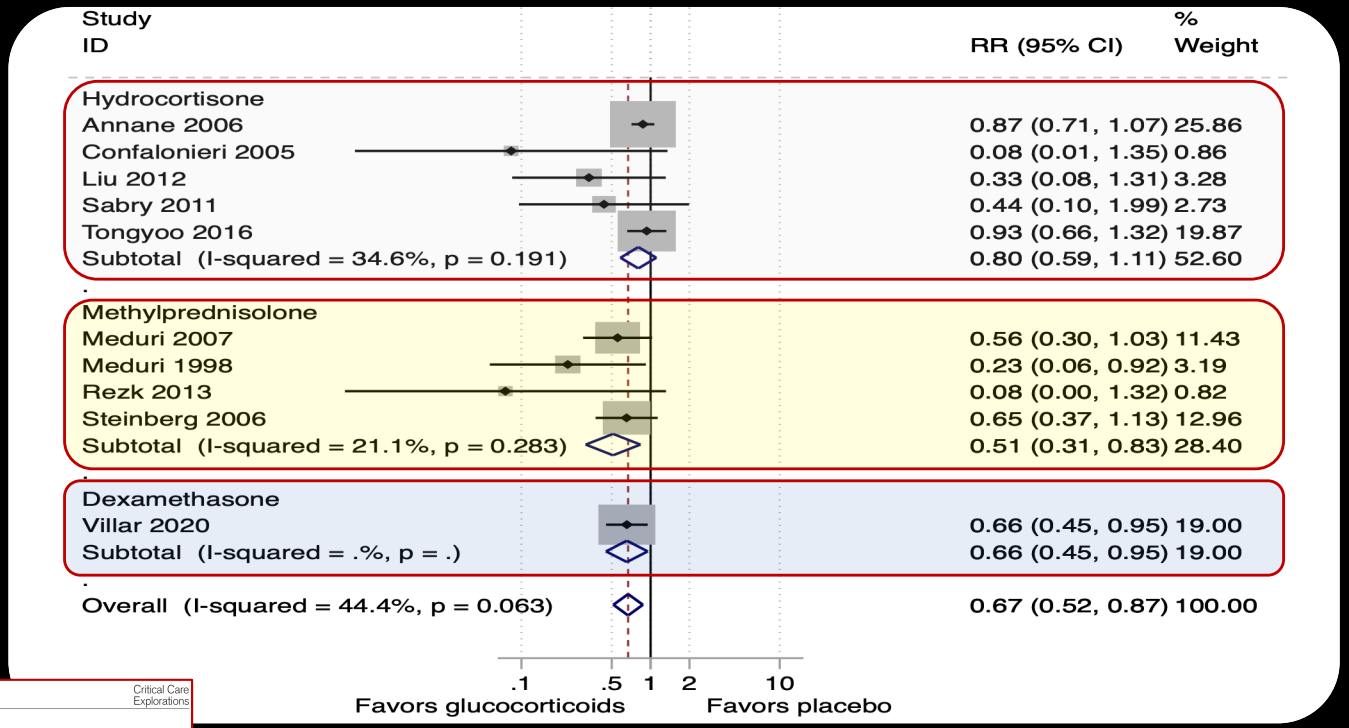
RCTs ARDS–GC Rx: Hsp. Mortality



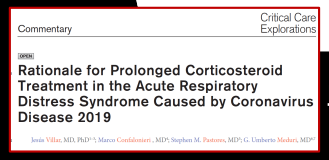
* Study design favored the placebo group
NNT: Early ARDS = 4.5; Late ARDS = 6.0

NNT = 6.5 for *60-day mortality*

RCTs ARDS–GC Rx: Hsp. Mortality



N=	Number needed to save one life
494	9.7 Hydrocortisone
272	5.3 Methylprednisolone
277	8* Dexamethasone
1043	7.2 Aggregate

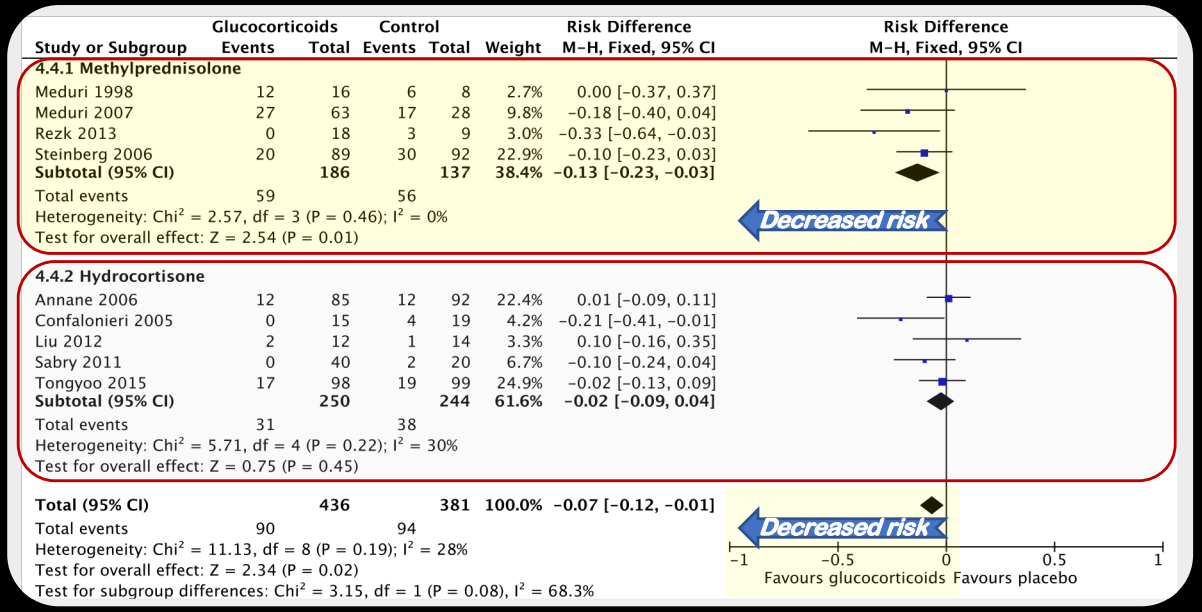

Commentary
Critical Care Explorations
Rationale for Prolonged Corticosteroid Treatment in the Acute Respiratory Distress Syndrome Caused by Coronavirus Disease 2019

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 ▶

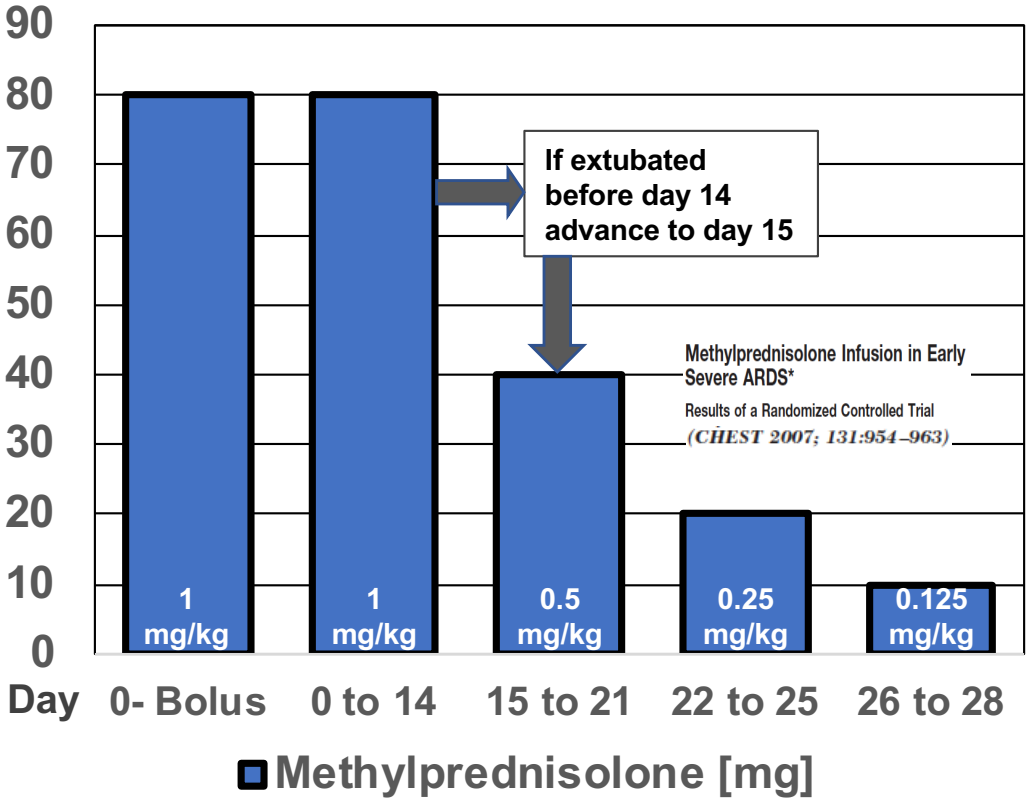


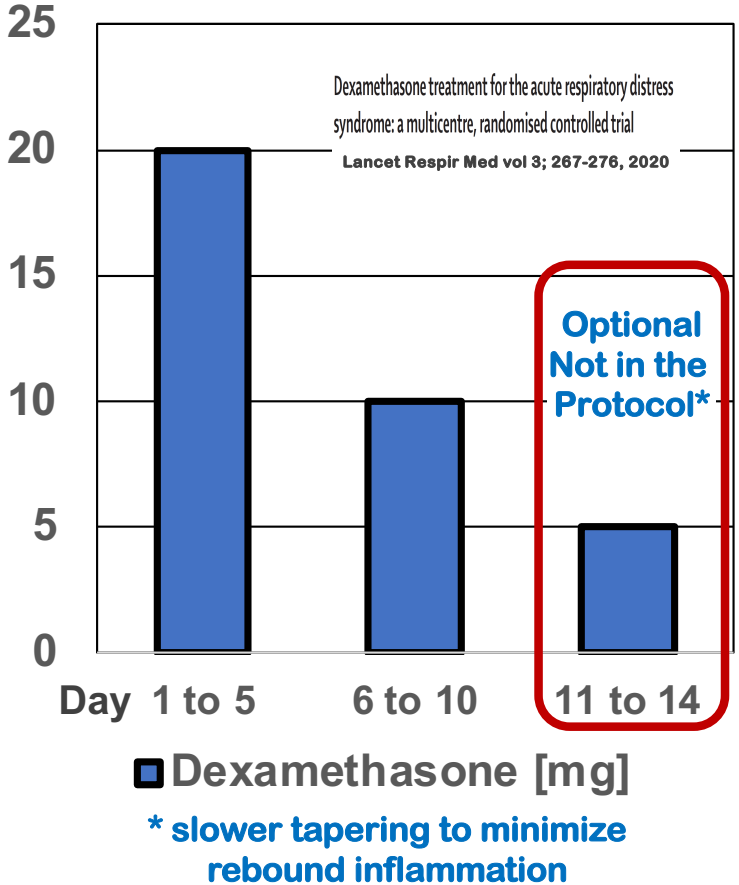
* Transient hyperglycemia does not impact outcome

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

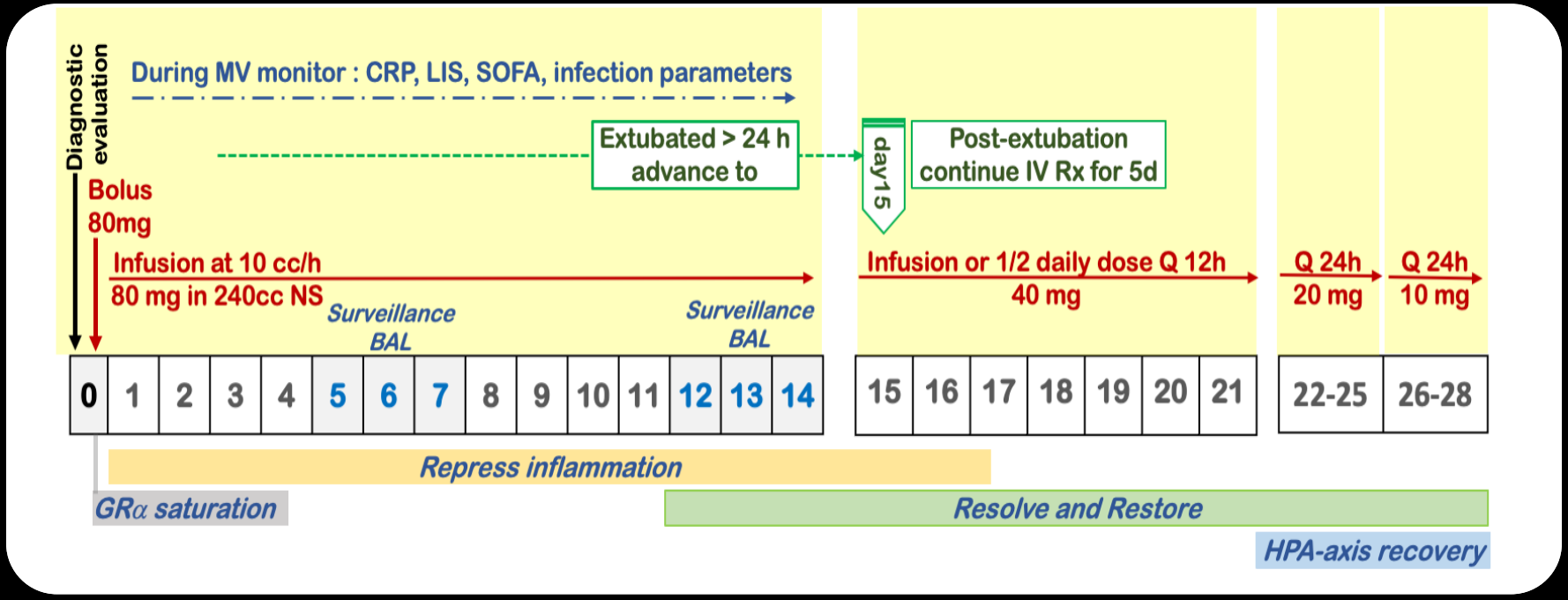




* slower tapering to minimize rebound inflammation

Methylprednisolone Rx Protocol

❑ **Protocol recommended by the 2017 by SCCM and ESICM Task Force[1]**



1. Annane D, et al. Guidelines for the Diagnosis and Management of CIRCI in Critically Ill Patients (Part I): *Critical care medicine.* 2017;45(12):2078-2088.

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?

Next

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

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

Study or Subgroup	log[Ratio of Means]	SE	Complicated Total	Non-Complicated Total	Weight	Ratio of Means IV, Random, 95% CI
Chen et al. 2020a	0.75030559	0.01700847	14	15	16.7%	2.12 [2.05, 2.19]
Diao et al. 2020	1.2861085	0.01523892	20	479	16.7%	3.62 [3.51, 3.73]
Huang et al. 2020a	1.03489647	0.08752466	13	28	16.6%	2.81 [2.37, 3.34]
Liu 2020	2.69261639	0.00539448	69	11	16.7%	14.77 [14.61, 14.93]
Qin et al. 2020	0.42527895	0.0036103	286	166	16.7%	1.53 [1.52, 1.54]
Wu et al. 2020	0.20490848	0.00385624	84	117	16.7%	1.23 [1.22, 1.24]
Total (95% CI)			**486**	**816**	**100.0%**	**2.90 [1.17, 7.19]**

Heterogeneity: $Tau^2 = 1.28$; $Chi^2 = 158694.72$, df = 5 ($P < 0.00001$); $I^2 = 100\%$
Test for overall effect: Z = 2.30 (P = 0.02)

Ratio of Means IV, Random, 95% CI
0.1 0.2 0.5 1 2 5 10
Higher in non-complicated Higher in complicated

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

Study or Subgroup	log[Ratio of Means]	SE	Complicated Total	Non-Complicated Total	Weight	Ratio of Means IV, Random, 95% CI
Diao et al. 2020	1.2861085	0.01523892	20	479	55.9%	3.62 [3.51, 3.73]
Huang et al. 2020a	1.03489647	0.08752466	13	28	44.1%	2.81 [2.37, 3.34]
Total (95% CI)			**33**	**507**	**100.0%**	**3.24 [2.54, 4.14]**

Heterogeneity: $Tau^2 = 0.03$; $Chi^2 = 8.00$, df = 1 ($P = 0.005$); $I^2 = 87\%$
Test for overall effect: Z = 9.42 ($P < 0.00001$)

Ratio of Means IV, Random, 95% CI
0.2 0.5 1 2 5
Higher in non-ICU Higher in ICU

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

https://doi.org/10.1101/2020.03.30.20048058

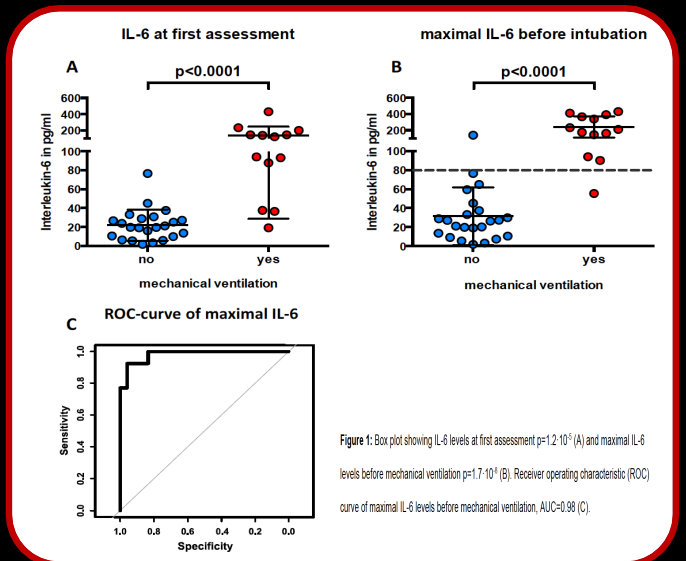


Figure 1: Box plot showing IL-6 levels at first assessment $p=1.2 \cdot 10^{-5}$ (A) and maximal IL-6 levels before mechanical ventilation $p=1.7 \cdot 10^{-4}$ (B). Receiver operating characteristic (ROC) curve of maximal IL-6 levels before mechanical ventilation, AUC=0.98 (C).

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

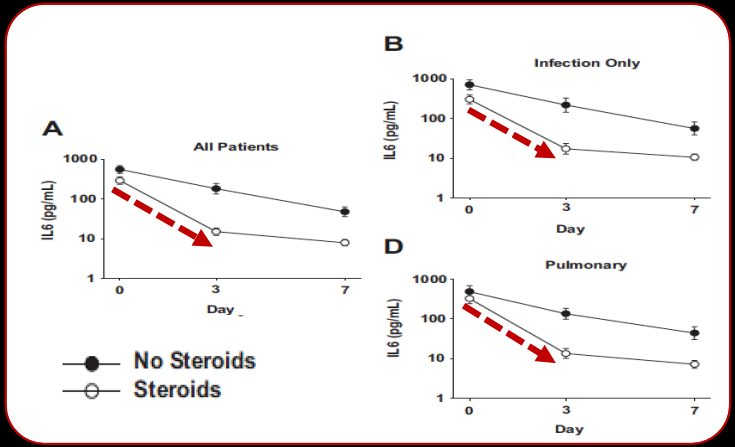
https://doi.org/10.1101/2020.04.01.20047381

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 …**

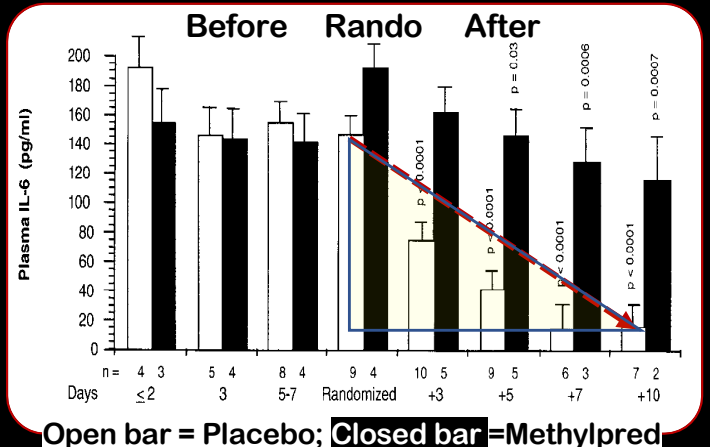
Early ARDS

Effects of methylprednisolone infusion on markers of inflammation, coagulation, and angiogenesis in early acute respiratory distress syndrome*



Late ARDS

Prolonged Methylprednisolone Treatment Suppresses Systemic Inflammation in Patients with Unresolving Acute Respiratory Distress Syndrome
Evidence for Inadequate Endogenous Glucocorticoid Secretion and Inflammation-induced Immune Cell Resistance to Glucocorticoids



Open bar = Placebo; Closed bar =Methylpred

1. Meduri GU, et al. **Plasma and BAL cytokine response to corticosteroid rescue treatment in late ARDS**. *Chest* 1995, **108**(5):1315-1325.
2. Meduri GU, et al. **Prolonged methylprednisolone treatment suppresses systemic inflammation in patients with unresolving ARDS**. *Am J Respir Crit Care Med* 2002, **165**(7):983-991.
3. Seam N, et al. **Effects of methylprednisolone infusion on markers of inflammation, coagulation, and angiogenesis in early ARDS**. *Critical Care Medicine* 2012, **40**(2):495-501.

Corticosteroid Treatment

1. **Non-viral ARDS:** 10 RCTs ▶ Evidence of safety & efficacy
2. **COVID-19 pneumonia**: WHO guidelines ◀ incomplete evidence
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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

World Health Organization. Coronavirus disease 2019 (COVID-19): situation report—54. March 14, 2020.

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[1]**
2. **2016 meta-analysis limited to 10 observational studies (< 1500 patients) most without reporting indications for CST details on timing, dose, and duration. [2]**
3. **Two retrospective observational studies without a pre-designed study protocol involving 600 patients with H1N1,[3] and 300 patients with MERS pneumonia[4]**
   - ❑ **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[4]: CST duration affected viral clearance: < 7 days = increased; > 7 days no impact! [detailed not mention in WHO document]**

That's IT

Clinical management of severe acute respiratory infection (SARI) when COVID-19 disease is suspected.

Interim guidance
13 March 2020

World Health Organization

1. Stockman et al SARS: systematic review of treatment effects. PLoS Med. 2006;3(9):e343.
2. Rodrigo C, et al. Corticosteroids as adjunctive therapy in the treatment of influenza. Cochrane Database Syst Rev. 2016
3. Delaney JW et al. The influence of corticosteroid treatment on the outcome of influenza A(H1N1pdm09)-related critical illness. Crit Care. 2016;20:75.
4. Arabi YM et al. Corticosteroid therapy for critically ill patients with Middle East respiratory syndrome. Am J Respir Crit Care Med. 2018;197(6):757-767.

Delayed viral clearance

- **Message**: What "kills" COVID-19 patients is dysregulated systemic inflammation. There is no evidence linking delayed viral clearance to worsened outcome in critically ill COVID-19 pts
- It is unlikely that delayed viral clearance would have a greater negative impact on outcome than the host own "cytokine storm" [1]

1. McAuley et al. COVID-19: consider cytokine storm syndromes and immunosuppression. *Lancet.* 2020.

2. Lancet Letters ◄ incomplete evidence

1

The effect of corticosteroids on mortality of patients with influenza pneumonia: a systematic review and meta-analysis

Yue-Nan Ni[1], Guo Chen[2], Jiankui Sun[3], Bin-Miao Liang[1*] and Zong-An Liang[1]

2

Treatment for severe acute respiratory distress syndrome from COVID-19

COVID-19.[9] Glucocorticoids should be avoided in view of the evidence that they can be harmful in cases of viral pneumonia and ARDS from influenza.[10] Rescue therapy with high-dose vitamin C can also be considered.[11]

3

Clinical evidence does not support corticosteroid treatment for 2019-nCoV lung injury

A 2019 systematic review and meta-analysis[9] identified ten observational studies in influenza, with a total of 6548 patients. The investigators found increased mortality in patients who were given corticosteroids (risk ratio [RR] 1·75, 95% CI 1·3–2·4; p=0·0002). Among

❑ **To justify lack of benefits ► Meta-analysis[1] of only 10 studies**

Six of ten without information on CS treatment!

Table 1 Characteristics of studies included in the present meta-analysis

Study ID	Study design	RCT no.	Population (corticosteroids/control)	Type of influenza	Type of corticosteroids	Initial dose of corticosteroids (mean ± SD)	Antiviral drug
Brun-Buisson [13]	Retrospective analysis	NR	83/125	H1N1	57.8% hydrocortisone 37.3% methylprednisolone 4.8% prednisone	328 ± 160 (equivalent hydrocortisone)	NR
Cao [15]	Retrospective study	NR	204/84	H7N9	91.7% methylprednisolone 3.9% dexamethasone 2.5% hydrocortisone 2.0% others	81.1 ± 83.2 (equivalent methylprednisolone)	Corticosteroids group: 201/204 Control group: 84/84
Diaz [12]	Prospective observational multicenter study	NR	136/236	H1N1	NR	NR	Corticosteroids group: 136/136 Control group: 236/236
Jung [16]	Multicenter retrospective study	NR	99/120	H1N1	NR	NR	Survivor: 130/141 Death: 68/78
Perez-Padilla [17]	Retrospective study	NR	7/11	H1N1	NR	NR	NR
Lee [18]	Cohort study	NR	264/817	H1N1	NR	NR	151 in all the patients
Li [19]	Case control	NR	1055/1086	H1N1	89.0% methylprednisolone 8.1% dexamethasone 2.0% hydrocortisone 0.9% prednisolone	141.3 ± 142 (equivalent methylprednisolone)	Corticosteroids: 1025/1055 Control group: 1022/1086
Moreno [20]	Secondary analysis of a prospective cohort study	NR	604/1242	Viral A/B/C	95.7% methylprednisolone; 3.8% prednisolone; 0.5% dexamethasone	A median (interquartile range) daily dose equivalent to 80 (60–120) mg of methylprednisolone	NR
Rois [21]	Multicenter prospective study	NR	75/103	H1N1	NR	NR	Survivors: 91/93 Death: 82/85
Viasus [22]	Observational, prospective cohort study	NR	37/160	H1N1	NR	NR	Corticosteroids group: 8/37 Control group: 41/160

NR not reported, *SD* standard deviation

1. 3.Ni YN, Chen G, Sun J, Liang BM, Liang ZA. The effect of corticosteroids on mortality of patients with influenza pneumonia: a systematic review and meta-analysis. *Crit Care.* 2019;23(1):99
2. Matthay MA, Aldrich JM, Gotts JE. Treatment for severe acute respiratory distress syndrome from COVID-19. *The Lancet Respiratory Medicine.* 2020.
3. Russell CD, Millar JE, Baillie JK. Clinical evidence does not support corticosteroid treatment for 2019-nCoV lung injury. *The Lancet.* 2020;395(10223):473-47

Corticosteroid Treatment

1. **Non-viral ARDS:** 10 RCTs ▶ Evidence of safety & efficacy
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3. CST-SARS pneumonia: 2 large studies

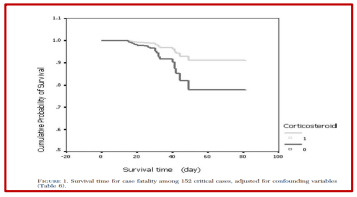
- Two large studies [n=401,1280]: overall no reduction in mortality
- **Subgroup analyses showed benefits**

Effective in *critical SARS* cases

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 (79.6%) 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 benefits 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.

Treatment of Severe Acute Respiratory Syndrome With Glucosteroids*

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



MP better than HC

Group				
No steroid (*N* = 99)	P (*N* = 170)	HC (*N* = 621)	MP (*N* = 177)	Pulse (*N* = 220)

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.

Corticosteroid treatment of severe acute respiratory syndrome in Hong Kong

Journal of Infection (2007) 54, 28–39

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 ≈ 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/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])

NEXT

1. Long Y, et al. Clinical recommendations from an observational study on MERS: glucocorticoids was benefit in treating SARS patients. *Int. J. Clin. Exp. Med.* 2016;9(5):8865-8873.
2. Li H, et al. Effect of low-to-moderate-dose corticosteroids on mortality of hospitalized adolescents and adults with influenza A(H1N1)pdm09 viral pneumonia. *Influenza Other Respir Viruses.* 2017;11(4):345-354.
3. Annane Det al. Guidelines for the Diagnosis and Management of Critical Illness-Related Corticosteroid Insufficiency (CIRCI) in Critically Ill Patients (Part I): SCCM and ESICM 2017. *Critical care medicine.* 2017;45(12):2078-2088.

4. CST-SARS : largest dataset n= 5327

- ❑ CST decreased mortality by 47% in severe cases
- ❑ Most effective protocol ≋ to one recommended by SCCM and ESICM TF[2]

Multivariate Cox regression analysis

adjustment for confounders

corticosteroid dose

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

80 mg

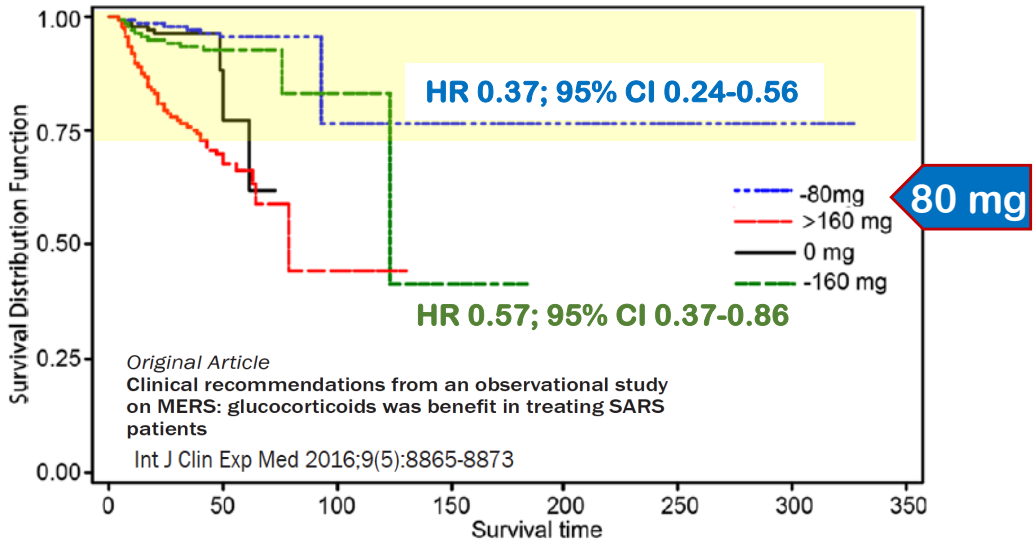


Figure 2. Survival curses on average daily GC doses in SARS patients.

Definition of severe SARS – any of 4: tachypnea (>20bpm); PaO_2 < 70mmHg; O_2 sat < 92%, sternum score >2

1. Long Y, et al. Clinical recommendations from an observational study on MERS: glucocorticoids was benefit in treating SARS patients. *Int. J. Clin. Exp. Med.* 2016;9(5):8865-8873.
2. Annane D, et al. Guidelines for the Diagnosis and Management of CIRCI in Critically Ill Patients (Part I): *Critical care medicine.* 2017;45(12):2078-2088.

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.

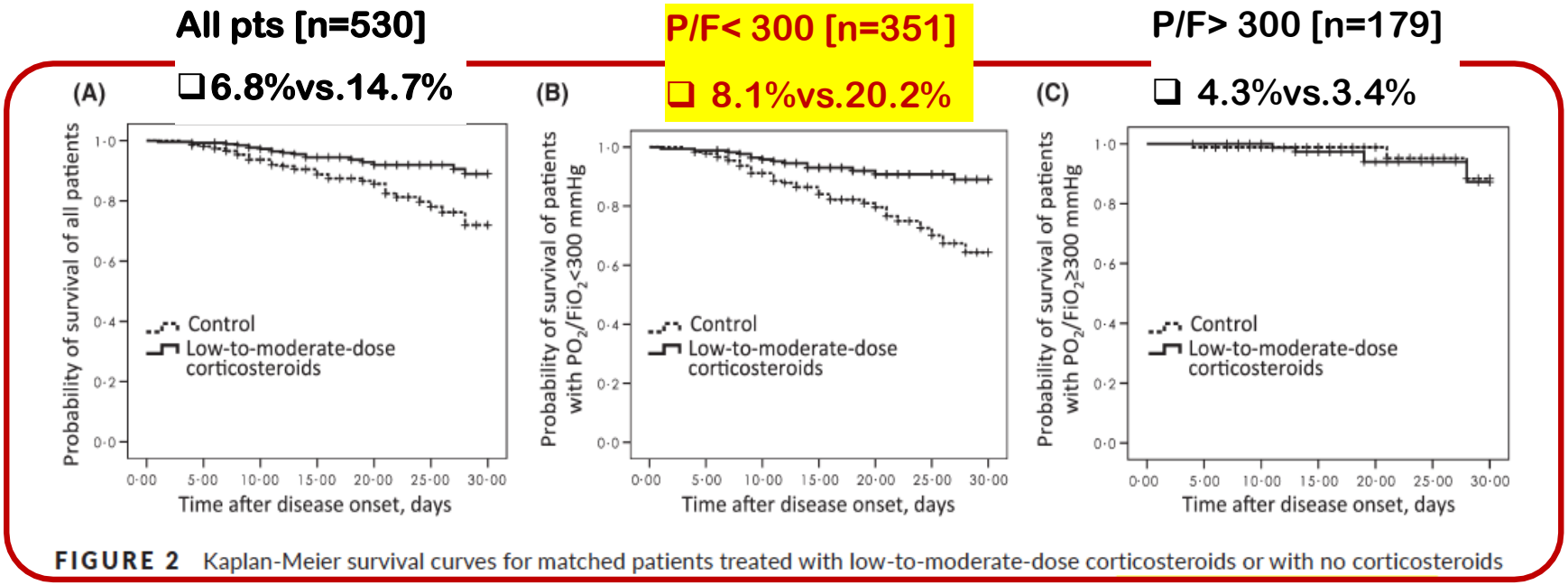


FIGURE 2 Kaplan-Meier survival curves for matched patients treated with low-to-moderate-dose corticosteroids or with no corticosteroids

H Li *et al*: **Effect of low-to-moderate-dose corticosteroids on mortality of hospitalized adolescents and adults with influenza A(H1N1)pdm09 viral pneumonia**. *Influenza Other Respir Viruses* 2017, **11**(4):345-354

Corticosteroid Treatment

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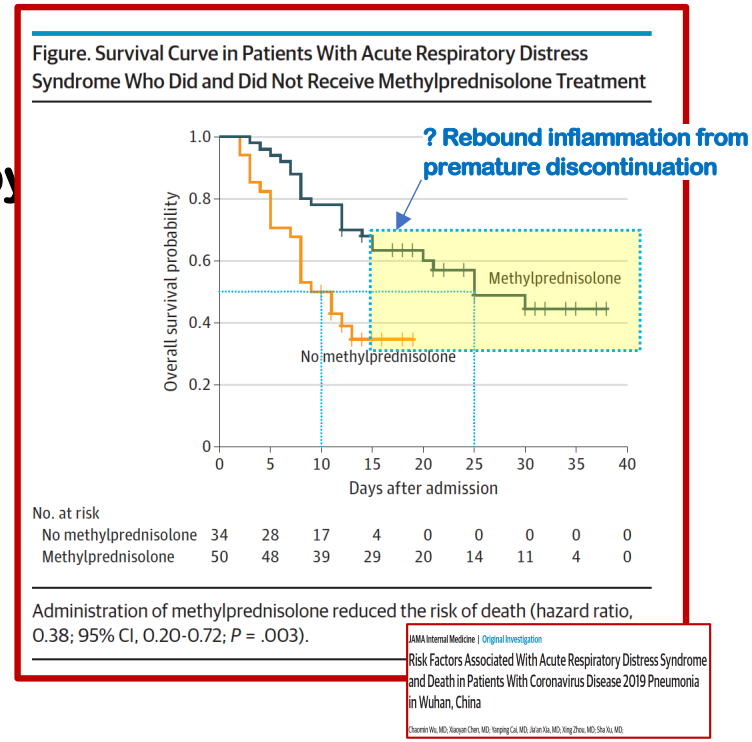
CST-COVID-19: early promising results

- ❑ 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]



1. Wu C, *et al*: Risk Factors Associated With Acute Respiratory Distress Syndrome and Death in Patients With Coronavirus Disease 2019 Pneumonia in Wuhan, China. *JAMA Intern Med* Published online March 13, 2020.
2. Annane D, et al. Guidelines for the Diagnosis and Management of CIRCI in Critically Ill Patients (Part I): *Critical care medicine.* 2017;45(12):2078-2088

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►

1.Accurate and timely identification of clinical features in severe risks, and early and appropriate intervention can block disease progression. 2.Appropriate dose of methylprednisolone can effectively avoid invasive mechanical ventilation and reduce case fatality rate in critical COVID-19 patients.

- ❑ No impact on neg. conversion

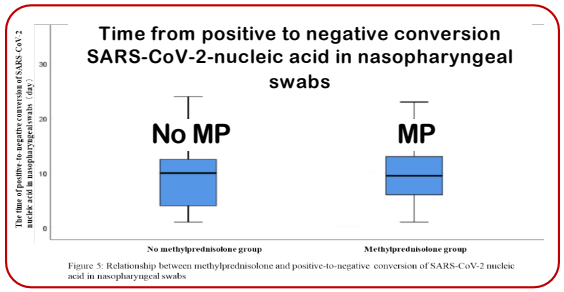
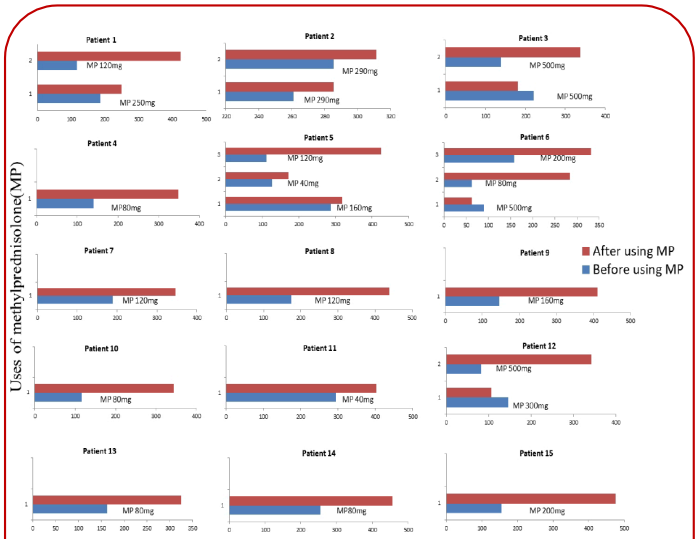


Figure 5: Relationship between methylprednisolone and positive-to-negative conversion of SARS-CoV-2 nucleic acid in nasopharyngeal swabs



PaO_2: FiO_2 before and after MP

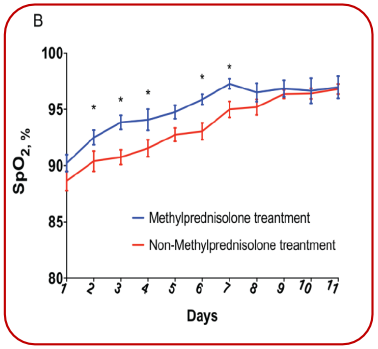
Key to successful treatment of COVID-19: accurate identification of severe risks and early intervention of disease progression

Meizhu Chen[1*],Changli Tu[1*],Cuiyan Tan[1],Xiaobin Zheng[1], Xiaohua Wang[3], Jian

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



Early, low-dose and short-term application of corticosteroid treatment in patients with severe COVID-19 pneumonia: single-center experience from Wuhan, China

Yin Wang[1], Weiwei Jiang[3], Qi He[3], Cheng Wang[4], Baoju Liu[2], Pan Zhou[5], Nianguo Dong[1], Qiaoxia Tong[2]

medRxiv preprint doi: https://doi.org/10.1101/2020.03.06.20032342.

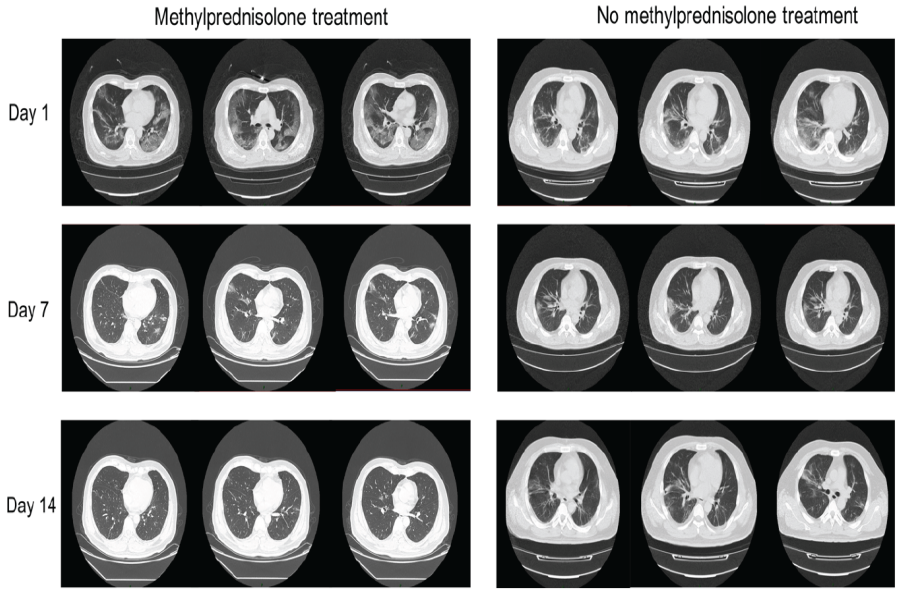


Figure 3 Images of chest CT scan on day 1, 7 and 14 after hospitalization in severe COVID-19 pneumonia patients with and without methylprednisolone treatment

Corticosteroid Treatment

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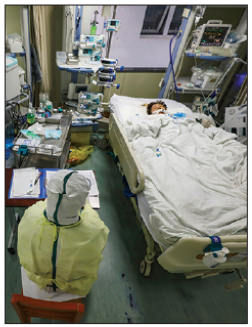
5. National Recommendations

❑ China

On the use of corticosteroids for 2019-nCoV pneumonia

*Lianhan Shang, Jianping Zhao, Yi Hu, Ronghui Du, *Bin Cao*



Barcroft Media/Contributor/Getty Images

Published Online
February 11, 2020
https://doi.org/10.1016/
S0140-6736(20)30361-5

For the Chinese translation see Online for appendix

❑ Italy

pagepress

National Institute for the Infectious Diseases "L. Spallanzani", IRCCS. Recommendations for COVID-19 clinical management

Emanuele Nicastri, Nicola Petrosillo, Tommaso Ascoli Bartoli, Luciana Lepore, Annalisa Mondi, Fabrizio Palmieri, Gianpiero D'Offizi, Luisa Marchioni, Silvia Murachelli, Giuseppe Ippolito, Andrea Antinori for the INMI COVID-19 Treatment Group (ICOTREG)*

National Institute for Infectious Diseases "L. Spallanzani", IRCCS, Rome, Italy

Supportive therapy:

- O_2 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)

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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*

Datasets [n=9149]

  - **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 PaO_2:FiO_2 < 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 > 100mg/L
- **Day 1**: MP 80mg bolus, …. ***followed by***
- **Continuous infusion** MP 80mg for [1] ≥ 8 days ***AND*** [2] P/F > 350 ***OR*** CRP ≤20mg/ L
- **Switch to oral** MP 16mg BID* UNTIL [1] CPR < 20% normal ***OR*** [2] P/F > 400 OR O2 sat ≥95% on RA …. ***followed by***
- **Slow taper** over 6 days [16 mg QD x 3 d, QD x 3 d]

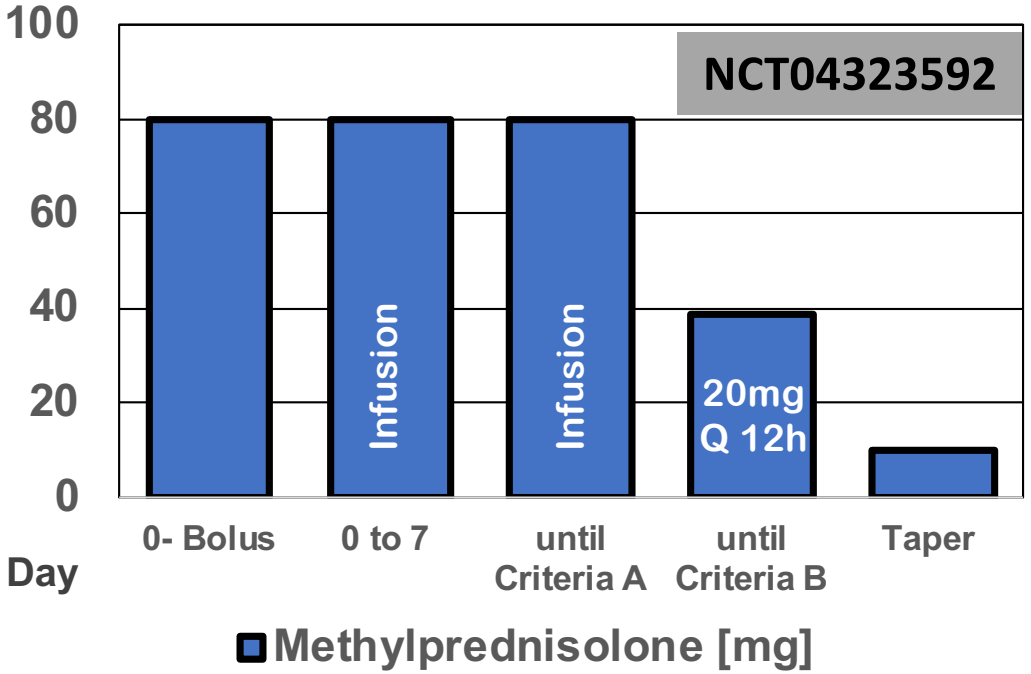
* Prof. Marco Confalonieri - Trieste Italy

NCT04323592*

* If NPO > or MP 20mg IV BID

Early Intervention ▶Prevent MV

❑Early Rx intervention: shorter guided duration



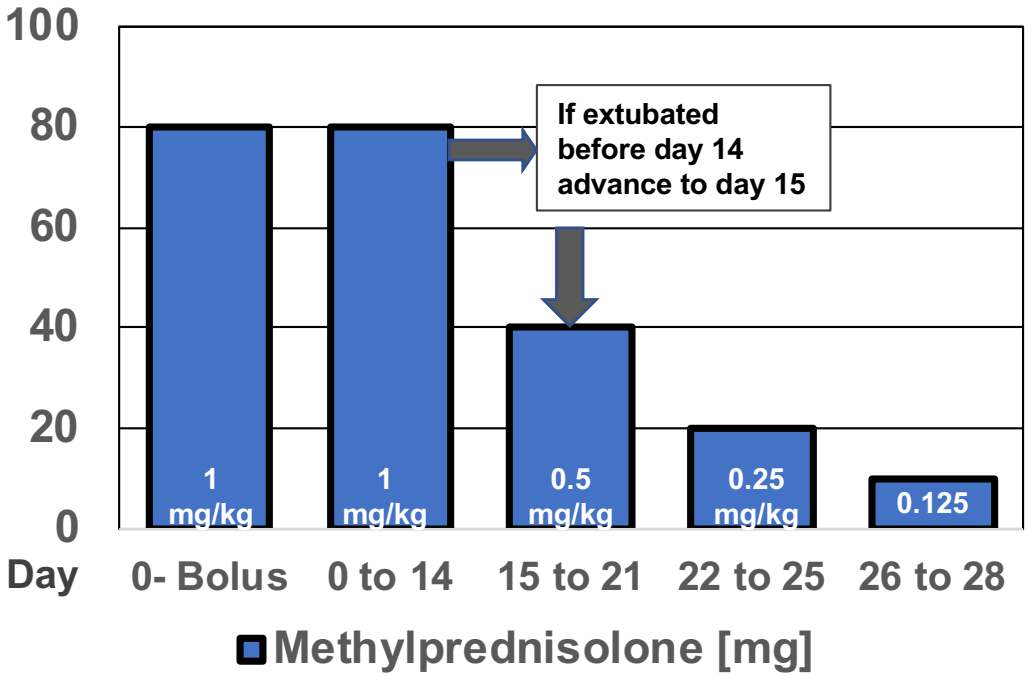
- ❑ Criteria A
  - ❑ PaO2/FiO2 > 350 or
  - ❑ CRP < 20mg/L
- ❑ Criteria B
  - ❑ PaO2/FiO2 > 400* or
  - ❑ CRP < 20% normal

* or $SatHbO_2$ ≥95% on ambient air

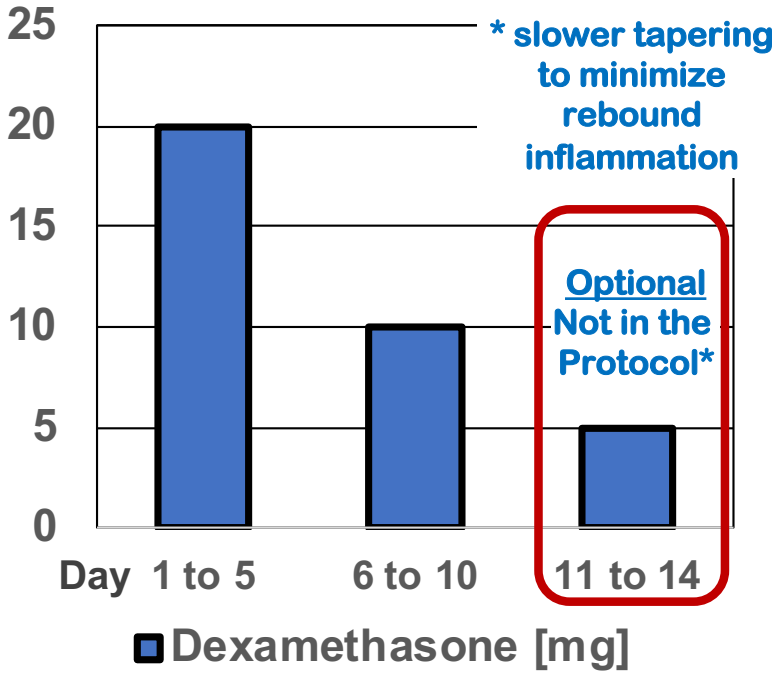
* Prof. Marco Confalonieri - Trieste Italy

COVID-19 on Mechan. Ventilation

❑ Both interventions are highly effective



Meduri Guet al: **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.** *Intensive Care Med* 2016, **42**(5):829-840.



Villar J *et al*. **Dexamethasone treatment for the acute respiratory distress syndrome: a multicentre, randomised controlled trial.** *The Lancet Respiratory medicine* 2020.

Haemophagocytic lymphohistiocytosis HLH

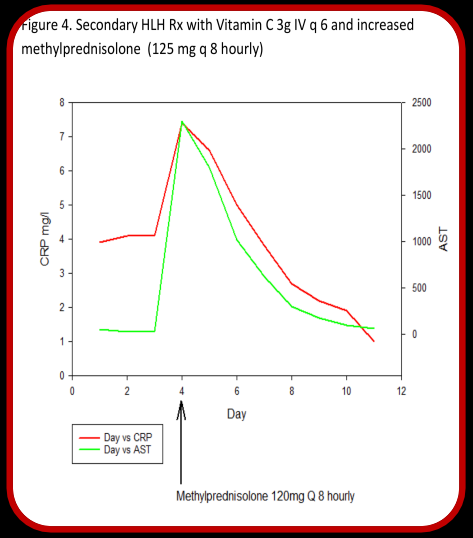
- CTL* fail to eliminate Ag presenting activated macrophages
- Activated macrophages [~~downregulation~~] ► *Cytokine storm*
  - ▲▲ TNF-α, IL-1β, IL-6, IL-8, IL-10 ……
- Laboratory findings:
  - ▲▲ serum ferritin [5,000 - >10,000], CRP ◄*acute phase reaction*
  - ▲ LFT: AST, ALT, LDH, bil., triglycerides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

*CTL = Cytotoxic lymphocytes that lyse macrophages bearing foreign antigen

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

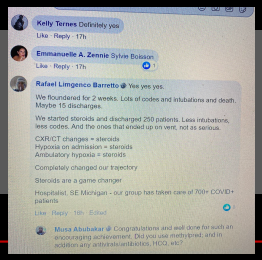


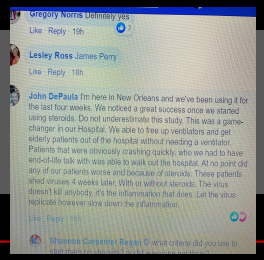
EVMS
MEDICAL GROUP
EVMS CRITICAL CARE
COVID-19 MANAGEMENT PROTOCOL
Developed and updated by Paul Marik, MD
Chief of Pulmonary and Critical Care Medicine
Eastern Virginia Medical School, Norfolk, VA
April 20th, 2020

https://www.evms.edu/media/evms_public/departments/internal_medicine/EVMS_Critical_Care_COVID-19_Protocol.pdf

Face Book 4-16-2020

https://www.facebook.com/groups/287062392273490/permalink/3121475630983306





❑ 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

Commentary

Critical Care Explorations

OPEN

Rationale for Prolonged Corticosteroid Treatment in the Acute Respiratory Distress Syndrome Caused by Coronavirus Disease 2019

Jesús Villar, MD, PhD[1–3]; Marco Confalonieri , MD[4]; Stephen M. Pastores, MD, MACP, FCCP, FCCM[5]; G. Umberto Meduri, MD[6,7]

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"