

COVID 19

Adjunctive therapy: Corticosteroids

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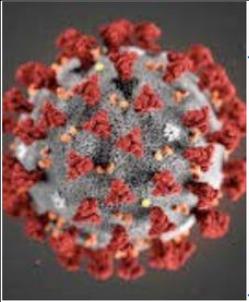
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COVID 19 TRAINING OF TRAINERS

**Organized by: ORHB, Universities in Oromia, ORHB AC, OPA, IOHPA, EEHA,
EEA**

26/4/20



OUTLINE

- **Introduction**
- **Corticosteroids role in pathogenesis**
- **Review of recommendations**
- **Conclusion**



World Map



NEW



U.S. Map



Critical Trends



COVID-19 Dashboard by the Center for Systems Science and Engineering (CSSE) at Johns Hopkins Universit...



Total Confirmed

2,897,645

Confirmed Cases by
Country/Region/Sovereignty

939,053 US

223,759 Spain

195,351 Italy

161,644 France

156,513 Germany

149,569 United Kingdom



Esri FAO NOAA

Total Deaths

202,880

26,384 deaths
Italy

22,902 deaths
Spain

22,614 deaths
France

20,319 deaths
United Kingdom

Deaths

Recovered

Total Test Conducted in U.S.

5,184,635

777,568 tested
New York US

506,035 tested
California US

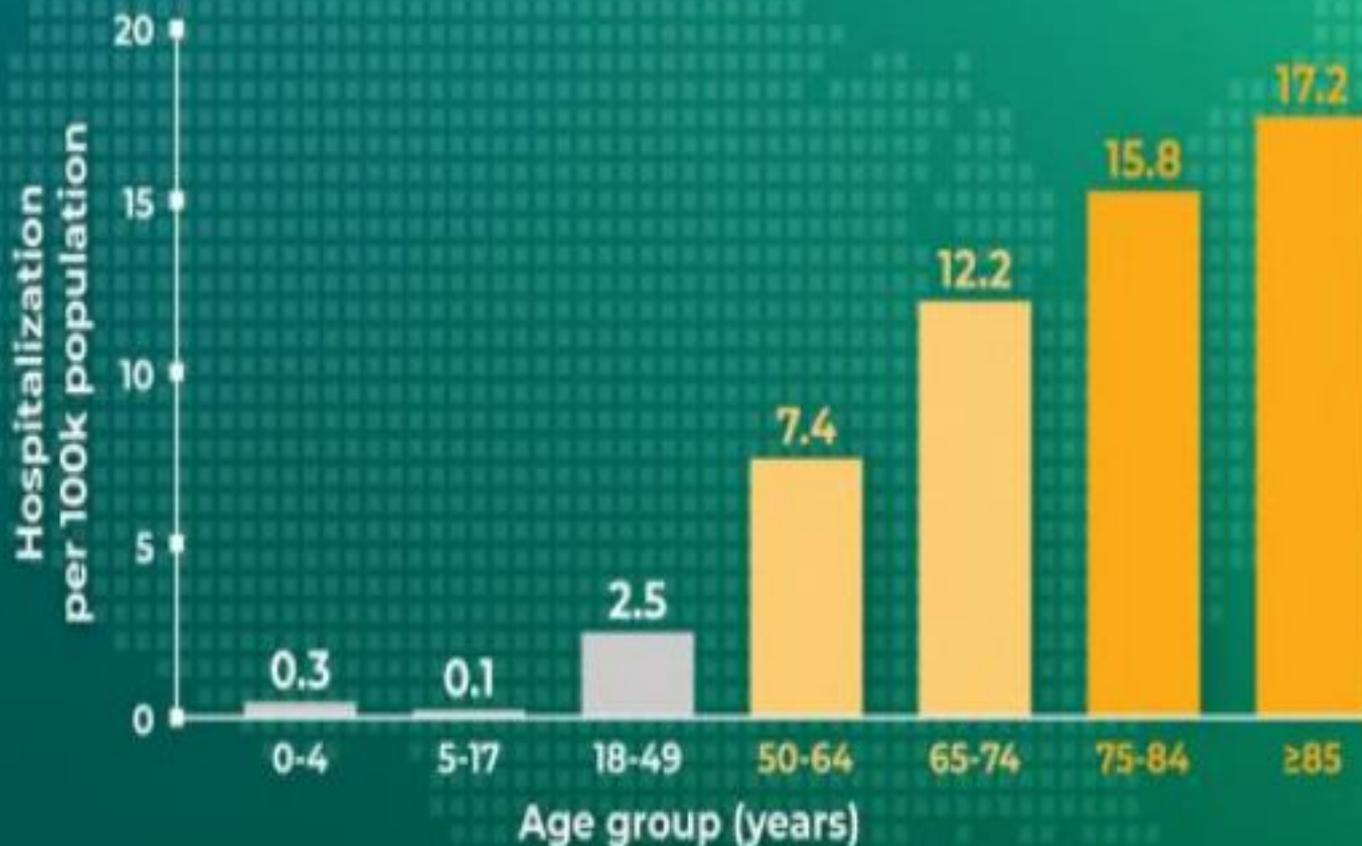
333,099 tested
Florida US

262,816 tested
Texas US

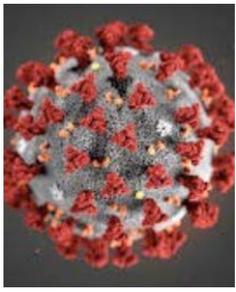
US Tested



RATES OF HOSPITALIZATION FOR COVID-19 INCREASE WITH AGE

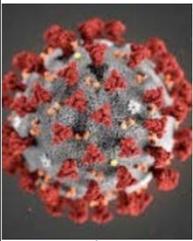


Everyone, especially older adults, should: ✓ stay home
✓ use face coverings in public settings ✓ wash hands frequently



Data on mortality

- **Mortality among all infected patients : 0.5% to 4%**
- **Among hospitalization, mortality : 5% to 15%**
- **Critically ill, a wide mortality range:22% to 62% in the early Hubei Province case series.**
- **The exact cause of death is unclear :progressive hypoxia and multiorgan dysfunction being the presumed causes.**



ARDS pathogenesis and correlation with CORTICOSTEROIDS

- **Experimental and clinical evidence:**
 - A strong cause and effect relationship between persistence in systemic inflammation and progression (unresolving) of ARDS.
- **Unresolving ARDS at the cellular level:**
 - Inadequate GC-GC receptor (GR)-mediated downregulation of inflammatory transcription factor nuclear factor- κ B (NF- κ B) despite elevated levels of circulating cortisol, (*critical-illness-related corticosteroid insufficiency (CIRCI)*) ^(1,2)

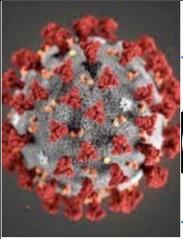
1. Meduri GU, Muthiah MP, Carratu P, Eltorky M, Chrousos GP. Nuclear factor-kappaB- and glucocorticoid receptor alpha-mediated mechanisms in the regulation of systemic and pulmonary inflammation during sepsis and acute respiratory distress syndrome. Evidence for inflammation-induced target tissue resistance to glucocorticoids. *Neuroimmunomodulation*. 2005;12:321–338. [[PubMed: 16557033](#)]
2. Marik PE, Pastores SM, Annane D, Meduri GU, Arlt W, Sprung CL, Keh D. Recommendations for the diagnosis and management of corticosteroid insufficiency in critically ill adult patients: consensus statements from an international task force by the American College of Critical Care Medicine. *Crit Care Med*. 2008;36:1937–1949. [[PubMed: 18496365](#)]



ARDS pathogenesis and correlation with CORTICOSTEROIDS

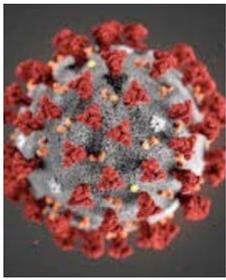
- **Systemic and bronchoalveolar lavage (BAL) levels of inflammatory mediators, markers of fibrogenesis, and ACM permeability.**
 - Persistent elevation in unresolving ARDS
- **Uninhibited increased NF- κ B activation at the tissue level:**
 - Ongoing tissue injury, intravascular and extravascular coagulation, and proliferation of mesenchymal cells, resulting in maladaptive lung repair and ultimately end-organ dysfunction and failure. ⁽¹⁾
- **The ability of activated GC-GR to downregulate systemic inflammation and restore tissue homeostasis can be significantly enhanced with exogenous GC treatment.**⁽²⁾

1. Meduri GU, Muthiah MP, Carratu P, Eltorky M, Chrousos GP. Nuclear factor-kappaB- and glucocorticoid receptor alpha-mediated mechanisms in the regulation of systemic and pulmonary inflammation during sepsis and acute respiratory distress syndrome. Evidence for inflammation-induced target tissue resistance to glucocorticoids. *Neuroimmunomodulation*. 2005;12:321–338. [[PubMed: 16557033](#)]
2. Meduri GU, Tolley EA, Chrousos GP, Stentz F. 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. *Am J Respir Crit Care Med*. 2002;165:983–991. [[PubMed: 11934726](#)]



Clinical Management and Outcomes

- **Management is not different from management of most viral pneumonia causing respiratory failure**
- **The principal feature is the development of ARDS: acute onset of hypoxemic respiratory failure with bilateral infiltrates.**
- **Evidence-based treatment guidelines for ARDS should be followed:**
 - **Conservative fluid strategies for patients without shock following initial resuscitation**
 - **Empirical early antibiotics for suspected bacterial co-infection until a specific diagnosis is made**
 - **Lung-protective ventilation**
 - **Prone positioning**
 - **Secretion management**
 - **Avoid bronchoscopy, nebs**
 - **Replete electrolytes, monitor I/Os strictly**
 - **Enteral nutrition as appropriate**



Drugs

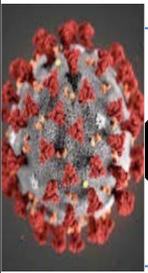
- **Antivirals**
 - Ritonavir / Lopinavir (Kaletra)
 - Hydroxychloroquine /chloroquine
 - Remdesevir
- **Antibiotics: Azithromycin**
- **IL-6 therapy**
- **Anti-inflammatory drugs**
 - Steroids, NO strong evidence to recommend routinely
 - NSAIDs are controversial



Corticosteroids: benefits Vs harms

- **A systematic review of observational studies of corticosteroids administered to patients with SARS:**
 - **No survival benefit**
 - **Possible harms**
 - Avascular necrosis
 - Psychosis
 - Diabetes
 - Delayed viral clearance (1).
- **Systematic review of observational studies in influenza:**
 - **Higher risk of mortality and secondary infections**
 - **Very low to low quality evidence owing to confounding by indication (2)**

1. Stockman LJ, Bellamy R, Garner P. SARS: systematic review of treatment effects. PLoS Med. 2006;3(9):e343. Epub 2006/09/14. doi: 10.1371/journal.pmed.0030343. PubMed PMID: 16968120; PMCID: PMC1564166.
2. Rodrigo C, Leonardi-Bee J, Nguyen-Van-Tam J, Lim WS. Corticosteroids as adjunctive therapy in the treatment of influenza. Cochrane Database Syst Rev. 2016;3:CD010406. Epub 2016/03/08. doi: 10.1002/14651858.CD010406.pub2. PubMed PMID: 26950335.

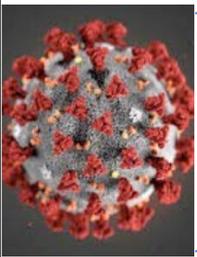


Corticosteroids: benefits Vs harms

- **A subsequent study that addressed the limitation by adjusting for time-varying confounders:**
 - No effect on mortality ⁽¹⁾.
- **A recent study of patients receiving corticosteroids for MERS used a similar statistical approach**
 - No effect on mortality but delayed LRT clearance of MERS-CoV ⁽²⁾

1. Delaney JW, Pinto R, Long J, Lamontagne F, Adhikari NK, Kumar A et al. The influence of corticosteroid treatment on the outcome of influenza A(H1N1pdm09)-related critical illness. *Crit Care*. 2016;20:75. Epub 2016/04/03. doi: 10.1186/s13054-016-1230-8. PubMed PMID: 27036638; PMCID: PMC4818504.

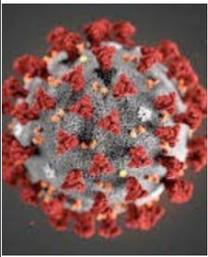
2. Arabi YM, Mandourah Y, Al-Hameed F, Sindi AA, Almekhlafi GA, Hussein MA et al. Corticosteroid therapy for critically ill patients with Middle East respiratory syndrome. *Am J Respir Crit Care Med*. 2018;197(6):757-767. doi: 10.1164/rccm.201706-1172OC. PMID: 29161116



Corticosteroids: benefits Vs harms

WHO recommendation

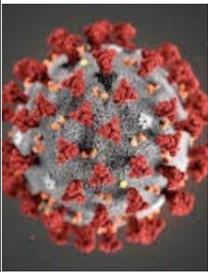
- **Given the lack of effectiveness and possible harm, routine corticosteroids should be avoided unless they are indicated for another reason**
 - **Exacerbation of asthma or COPD**
 - **Septic shock**
- **Risk/benefit analysis needs to be conducted for individual patients**



Corticosteroids and sepsis

- **An international panel recent guideline: based on the findings of two recent large RCTs**
 - **A conditional recommendation for corticosteroids for all patients with sepsis (including septic shock) ⁽¹⁾**
- **Surviving Sepsis guidelines:**
 - **Recommend corticosteroids only for patients in whom adequate fluids and vasopressor therapy do not restore hemodynamic stability ⁽²⁾, written before the above RCTs were reported**

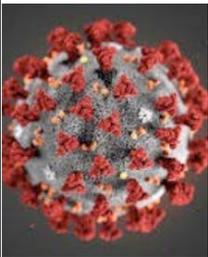
1. Lamontagne F, Rochweg B, Lytvyn L, Guyatt GH, Moller MH, Annane D et al. Corticosteroid therapy for sepsis: a clinical practice guideline. *BMJ*. 2018;362:k3284. Epub 2018/08/12. doi: 10.1136/bmj.k3284. PubMed PMID: 30097460.
2. Rhodes A, Evans LE, Alhazzani W, Levy MM, Antonelli M, Ferrer R et al. Surviving Sepsis Campaign: International Guidelines for Management of Sepsis and Septic Shock: 2016. *Intensive Care Med*. 2017;43(3):304-77. Epub 2017/01/20. doi: 10.1007/s00134-017-4683-6. PubMed PMID: 28101605



CORTICOSTEROIDS IN COVID 19 & SEPSIS

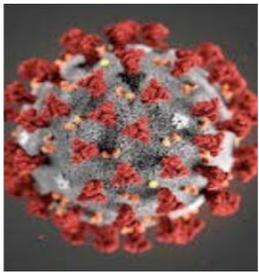
- **Must balance the potential small reduction in mortality with the potential downside of prolonged shedding of coronavirus in the respiratory tract observed in patients with MERS ⁽¹⁾**
- **Monitor and treat:**
 - **Hyperglycaemia**
 - **Hypernatraemia, and**
 - **Hypokalaemia if corticosteroids are given**
- **Monitor for recurrence of inflammation and signs of adrenal insufficiency after stopping corticosteroids, which may have to be tapered.**
- **Because of the risk of strongyloides stercoralis hyper-infection with steroid therapy, diagnosis or empiric treatment should be considered in endemic areas if steroids are used ⁽²⁾.**

1. Arabi YM, Mandourah Y, Al-Hameed F, Sindi AA, Almekhlafi GA, Hussein MA et al. Corticosteroid therapy for critically ill patients with Middle East respiratory syndrome. *Am J Respir Crit Care Med.* 2018;197(6):757-767. doi: 10.1164/rccm.201706-1172OC. PMID: 29161116.
2. CDC. Resources for health professionals: parasites - strongyloides [website]. Washington (DC): Centers for Disease Control and Prevention (https://www.cdc.gov/parasites/strongyloides/health_professionals/index.html, accessed 4 March).



Pregnancy in COVID-19 & CORTICOSTEROID

- **WHO recommends**
 - Antenatal corticosteroid therapy for women at risk of preterm birth from 24 to 34 weeks of gestation when there is no clinical evidence of maternal infection, and adequate childbirth and newborn care is available.
 - Woman with mild COVID-19, the clinical benefits of antenatal corticosteroid might outweigh the risks of potential harm to the mother.
 - In this situation, the balance of benefits and harms for the woman and the preterm newborn should be discussed with the woman to ensure an informed decision, as this assessment may vary depending on the woman's clinical condition, her wishes and that of her family, and available health care resources
- **WHO has prioritized the evaluation of corticosteroids in clinical trials to assess safety and efficacy**



Corticosteroids

- **Mixed data in SARS and MERS**
- **In COVID-19, one study suggested a decrease in mortality in patients with ARDS with receipt of steroids**
- **Methylprednisolone 1-2 mg/kg/day for 3-5 days**
- **Concern about delaying viral clearance**

Conclusion

- **Mixed results of corticosteroids use with COVID-19**
- **Corticosteroids may delay viral clearance**
- **Do not routinely give systemic corticosteroids for treatment of viral pneumonia outside clinical trials. (WHO recommendation)**

Thank you