## SARS-CoV-2 Treatment Evidence Tables
### Corticosteroids

<table>
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<th>Recommendation</th>
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| **Penn Medicine:** Based on data from the RECOVERY trial, we strongly recommend patients with severe COVID-19 disease who are on mechanical ventilation or ECMO receive dexamethasone 6mg PO/IV once daily for up to 10 days.  
  - Dexamethasone can be considered in patients on low-flow supplemental oxygen if the potential benefits are deemed to outweigh risks considering clinical trajectory, risk factors for progression, and comorbidities.  
  - We recommend against corticosteroids for COVID-19 patients not requiring supplemental oxygen, unless there are other compelling indications because there is no demonstrated benefit in this group of patients and potentially a trend toward harm.  
  - Dexamethasone should be used per the criteria outlined above for non-pregnant patients. ID and MFM should be consulted in all cases of pregnant patients requiring supplemental oxygen. Dose of dexamethasone may need to be increased for short courses to promote fetal lung maturity at the discretion of MFM  
    - Steroids may be considered in all cases regardless of need for supplemental oxygen to promote fetal lung maturity. These cases should be reviewed with MFM. | A multi-center, randomized, open-label trial among 6,416 patients in the UK found significantly lower 28-day mortality among patients who received dexamethasone (n=2,104). A mortality benefit was observed among patients requiring mechanical ventilation and non-invasive supplemental oxygen; however, no benefit was observed among patients who did not have any supplemental oxygen requirement. Among patients who received non-invasive supplemental oxygen, results were not stratified by level of support. A mortality benefit was also observed among patients who were >7 days from symptom onset.(1)  
  - A multi-center quasi-experimental study among 213 patients demonstrated a reduced rate of primary composite endpoint of death, ICU transfer or mechanical ventilation among patients who received early corticosteroids through institutional protocol.(2)  
  - Two retrospective cohort studies among COVID-19 patients who developed ARDS found that corticosteroid treatment was associated with a decreased risk of mortality.(3, 4) An additional retrospective review reported a decreased risk of intubation among patients receiving corticosteroids.(5)  
  - Retrospective observational study among 46 patients (26 receiving methylprednisolone) found quicker resolution in clinical symptoms among patients receiving early low-dose steroids.(6)  
  - Retrospective study among 206 patients reported that high-dose (80mg) corticosteroids were associated with prolonged viral shedding; this | No clinical trial data in SARS-CoV-2.  
  - Currently no definite evidence of benefit  
  - Retrospective observational study among 31 patients with mild disease found no benefit in time to viral clearance, resolution of symptoms, or discharge.(10)  
  - Descriptive studies of corticosteroids in SARS-CoV-2 do not suggest a clear benefit.(11, 12)  
  - Studies of corticosteroids in treating other viral illnesses including MERS, SARS, and influenza found no mortality benefit and noted reduced viral clearance in addition to other known corticosteroid side effects.(13-16) |

  - On the basis of the preliminary report from the Randomised Evaluation of COVID-19 Therapy (RECOVERY) trial, the Panel recommends using dexamethasone 6 mg per day for up to 10 days for the treatment of COVID-19 in patients who...*
are mechanically ventilated (AI) and in patients who require supplemental oxygen but who are not mechanically ventilated (BI).
- If dexamethasone is not available, the Panel recommends using alternative glucocorticoids such as prednisone, methylprednisolone, or hydrocortisone (AII).

**Infectious Diseases Society of America**
- Recommendation 4. Among hospitalized patients with severe* COVID-19, the IDSA guideline panel suggests glucocorticoids rather than no glucocorticoids. (Conditional recommendation, Moderate certainty of evidence)
  - Remark: Dexamethasone 6 mg IV or PO for 10 days (or until discharge if earlier) or equivalent glucocorticoid dose may be substituted if dexamethasone unavailable. Equivalent total daily doses of alternative glucocorticoids to dexamethasone 6 mg daily are methylprednisolone 32 mg and prednisone 40 mg.
  - *Severe illness is defined as patients with \( \text{SpO}_2 \leq 94\% \) on room air, and those who require supplemental oxygen, mechanical ventilation, or ECMO.
- Recommendation 5. Among hospitalized patients with COVID-19 without hypoxemia requiring supplemental oxygen, the IDSA guideline panel suggests against the use of glucocorticoids. (Conditional recommendation, Low certainty of evidence).

- Observational ‘before-and-after’s study performed in France after hospital guidelines changed to include corticosteroids found that steroids were associated with lower risk of death and ICU admission or death.(8)
- Case series among 6 patients with severe COVID-19 pneumonia with ARDS and laboratory evidence of hyper-inflammatory syndrome reported clinical improvement in all patients.(9)
# Corticosteroids Detailed Evidence Table

**Mechanism:** Theoretically reduces inflammatory-induced lung injury and reduces cytokine storm.

## Clinical Trials


<table>
<thead>
<tr>
<th>Question</th>
<th>Does a short course of corticosteroids in patients with COVID-19 may attenuate the excessive host respiratory and systemic inflammatory responses?</th>
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</table>
| Findings | Patients with moderate to severe COVID-19 in the early corticosteroid group had a reduced rate of primary composite endpoint of death, ICU transfer or mechanical ventilation (34.9% in early steroid protocol group vs 54.3% in pre-protocol group; p= 0.005)  
- Early corticosteroid initiation was independently associated with a reduction in the composite endpoint at 14 days (aOR: 0.41; 95% CI [0.22 – 0.77]) after adjusting for male sex, NEWS ≥7, and age ≥ 60  
- Median reduction in hospital LOS by 3 days in early group (p<0.001) |
| Setting & Design | Multi-center quasi-experimental study among 213 patients across 5 hospitals in Michigan between March 12, 2020 and March 27, 2020  
- Follow-up: 14 days after initial presentation  
- Patient data was censored on April 9, 2020  
- Compared outcomes for pts admitted before and after implementation of protocol for early corticosteroid therapy on March 20, 2020:  
  - Early corticosteroid group (n=132): March 20, 2020 - March 27, 2020  
    - 68.2% corticosteroid use  
  - Standard of care group (n=81): March 12, 2020 - March 19, 2020  
    - 56.8% corticosteroid use  
  - Early corticosteroid group received IV solumedrol 0.5 to 1mg/kg/d for 3 days (moderate) or 3-7 days (ICU pts)  
  - Standard of care group received standard care, comprised of supplemental oxygen, HFNC, invasive ventilation, antibiotic agents, vasopressor support, and renal-replacement therapy  
  - Antivirals: combination of lopinavir-ritonavir and ribavirin or hydroxychloroquine  
    - Lopinavir-ritonavir with ribavirin was removed from the COVID-19 institutional protocol on March 17, 2020  
    - Moderate COVID-19: hydroxychloroquine 400 mg twice daily for 2 doses on day 1, followed by 200 mg twice daily on days 2-5  
  - Compassionate use Remdesivir on requested for eligible mechanically ventilated patients  
  - Tocilizumab was administered on a case-by-case basis in ICU patients  
| Risk stratified by severity of symptoms on presentation to the hospital |  
- Mild: without hypoxia or exertional dyspnea  
  - Treated with symptom relief only and not admitted to the hospital  
- Moderate: infiltrates on chest radiography and required supplemental oxygen by nasal cannula or high flow nasal cannula  
- Severe: Respiratory failure requiring mechanical ventilation |
| Outcome |  
- Primary composite endpoint: escalation to ICU, progression to respiratory failure requiring mechanical ventilation, or in-hospital all-cause mortality  
- Secondary endpoints: development and severity of ARDS, days to ventilator liberation, shock, acute kidney injury (AKI), and length of hospital stay |
| Patient Population | Consecutive adult patients (age ≥18 years) hospitalized between March 12, 2020 through March 27, 2020 with COVID-19 infection  
- Inclusion criteria: Radiographic evidence of bilateral pulmonary infiltrates; required oxygen by nasal cannula, high-flow nasal cannula (HFNC), or mechanical ventilation  
- Exclusion criteria: Transferred from an out-of-system hospital, died within 24 hours of presentation to the ED, or were admitted < 24 hours |
### Limitations
Before-and-after study design during a rapidly evolving epidemic: clinicians became more experienced which could lead to improved outcomes
- Imbalance in baseline characteristics between the two groups (increased rate of COPD in pre-corticosteroid group)
- Confounding due to changes in antiviral regimens
- Confounding by indication

### Link


### Question
Does treatment with either lopinavir + ritonavir, hydroxychloroquine, corticosteroids, azithromycin, convalescent plasma or tocilizumab prevent death in hospitalized patients with COVID-19?

### Findings
- Significantly lower 28-day mortality in dexamethasone arm (482 patients [22.9%]) compared to standard care (1,110 patients [25.7%]; rate ratio, 0.83 [95% CI, 0.75-0.93]; P<0.001)
  - Level of respiratory support received at randomization (test for trend, p<0.001)
    - Greatest reduction among subgroup of patients receiving mechanical ventilation at baseline (rate ratio, 0.64 [95% CI, 0.51-0.81])
    - Patients receiving mechanical ventilation were younger and had longer symptom duration prior to randomization
    - Also demonstrated reduction among patients receiving non-invasive oxygen support at baseline (rate ratio, 0.82 [95% CI, 0.72-0.94])
    - No benefit observed among patients not receiving oxygen at baseline (rate ratio, 1.19 [95% CI 0.91-1.55])
  - Greatest reduction in 28-day mortality among patients with >7 days of symptoms at randomization (test for trend, p<0.001)
  - Shorter duration of hospitalization was observed in dexamethasone group than standard care (median 12 days vs. 13 days)
  - Dexamethasone associated with greater probability of discharge within 28 days (rate ratio, 1.10 [95% CI, 1.03-1.17])
  - Greatest decrease in length of stay among patients receiving invasive mechanical ventilation at baseline (test for trend, p=0.002)
- Composite outcome of death or mechanical ventilation among patients not on invasive mechanical ventilation at baseline:
  - Decreased risk of composite outcome among dexamethasone group (risk ratio, 0.91 [95% CI, 0.82-1.00]; p=0.049)
  - Significantly greater effects observed among patients receiving oxygen at randomization (test for trend, p=0.008)
  - Risk of progression to invasive mechanical ventilation was lower among those allocated to dexamethasone (risk ratio, 0.77 [95% CI, 0.62-0.95])

### Setting & Design
Recovery Trial (Randomised Evaluation of COVid-19 thERapY): randomized, open-label, adaptive platform trial comparing several possible treatments with usual care among 11,320 hospitalized patients with COVID-19 across 175 NHS hospitals in the UK between March 19 and June 8, 2020
- 9,355 (83%) were eligible to be randomized to dexamethasone, based on drug availability
- Web-based simple randomization (2:1 randomization to standard care or treatment) with allocation concealment
- Treatment (n=2,104): oral or IV dexamethasone 6 mg once daily for up to 10 days (or until discharge if sooner) + standard care
  - Equivalent to prednisone 40mg
  - Pregnancy or breastfeeding women: received oral prednisolone 40 mg daily or IV hydrocortisone 80 mg twice daily instead of dexamethasone
- Control (n=4,312): standard care
- Performed intention-to-treat (ITT) analyses
- 95% of patients in treatment arm received at least 1 dose of dexamethasone
  - Median number of days of treatment: 6 days
  - 7% of the usual care group received dexamethasone
  - Subgroup analyses: age, sex, level of respiratory support, days since symptom onset, and predicted 28-day mortality risk

### Outcome
- Primary: 28-day mortality
- Secondary: time to hospital discharge, requirement of invasive mechanical ventilation among patients not ventilated at baseline, death
Patient Population
Hospitalized patients with clinically-suspected or laboratory confirmed SARS-CoV-2 infection
• On May 9, 2020, age inclusion criteria of adults ≥18 was removed
• Pregnant or breast-feeding women were eligible for inclusion
• Exclusion: Attending clinician opinion that medical history may put the patient at significant risk

Limitations
Design:
• Exclusion criteria of attending clinician opinion regarding previous medical history is not clearly defined
• Drug availability varied across centers
• Potential recall bias: data collected via single online follow-up form was completed when participants were discharged, had died, or at 28 days after randomization (whichever occurred earlier)
• Did not differentiate between level of non-invasive ventilation at baseline, which is clinically meaningful
• 5% of patients had not completed study at time of analyses and were therefore censored
Generalizability: mostly males (64%), only 6 were pregnant
• No access to remdesivir before May 26, 2020
• Higher overall COVID-19 mortality rates in the UK compare to US
• Sicker and older patient population at baseline
Misclassification bias: only 82% had confirmed SARS-CoV-2
• 10% of patients had a negative RT-PCR and 9% had an unknown result
• Did not conduct sensitivity analyses using confirmed diagnoses

Intention to treat analysis
• Cross-over between treatment arms
  • Do not report as-treated analyses
• Variability in duration of dexamethasone treatment
• Confounding: 5% of patients were randomized to another treatment
Did not present data on adverse events, including secondary infection rates

Link
Patients also received antivirals (lopinavir/r or darunavir/r) and/or hydroxychloroquine, antibiotics, and anticoagulation.

| Outcome | • Death  
| • ICU admission or death before ICU admission |

| Patient Population | Patients with positive RT-PCR for COVID-19 or characteristic findings on chest radiography  
| • Exclusion: Patients with initiation of corticosteroid therapy during the transition period (from 21–25 March 2020)  
| o Patients with <7 days between symptom onset and 14 April 2020 |

| Limitations | • Small sample size  
| • Changes in therapies over time may confound findings  
| • Inclusion of patients with characteristic imaging but without positive COVID-19 test may result in misclassification of exposure  
| • Imbalance in baseline characteristics between groups |

| Link | [https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7342082/](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7342082/) |

**Question**
Are glucocorticoids efficacious in patients with cytokine-release syndrome due to COVID-19?

**Findings**
Trend towards improved survival and reduced intubation in the groups of patients where glucocorticoids were given, although none reached statistical significance.

**Setting & Design**
Retrospective observational study among 92 patients

- Median follow-up: 11 days
- Corticoids prescribed at 2 mg/kg/day for 3 days (n=30), 250 mg/day for 3 days (n=27), and 500 mg/day for 3 days (n=26)
- Corticosteroids alone (n=60 [65.2%])
- Corticosteroids + tocilizumab (n=23 [25%])
- Tocilizumab alone (n=9 [9.8%])

**Outcome**
Composite outcome of mortality & intubation

**Limitations**
- Manuscript in Spanish, preventing perfect translation
- Small sample size
- Corticosteroid dosing, stratified by receipt of tocilizumab, not described
- Confounding by indication
- Inadequate presentation of baseline characteristics to compare balance between groups

**Link**


**Question**
What is the effect of corticosteroids on hospitalized patients with COVID-19?

**Findings**
35 (50%) required mechanical ventilation, due to respiratory failure

- Corticosteroids decreased the risk of intubation: risk difference of -47.1% (95% CI, -71.8 to -22.5)
- Risk difference was similar using inverse probability weighting (ATE, -47.5% [95% CI, -70.0% to -25.0%])

**Setting & Design**
Retrospective review of all hospitalized patients (n=70) with COVID-19 on at least 3L of O2 between March 10 and April 9, 2020

- Propensity score 1:1 matching to the nearest neighbor with a caliper of 0.25
- Sensitivity analysis: Inverse probability weighting with the propensity score

**Outcome**
Oro-tracheal intubation

**Limitations**
Letter to the editor: methods and detailed results not presented

**Question**
Can steroid use can improve the mortality of patients with COVID-19 pneumonia?

**Findings**
Corticosteroid use was associated with lower in-hospital mortality (13.9% vs 23.9%; HR 0.51 [95% CI, 0.27-0.96]; p=0.044)
- Among patients with moderate or severe ARDS, in-hospital mortality was lower among patients treated with steroids (26.2% versus 60%; OR, 0.23 [95% CI, 0.08-0.71]; p=0.014)
- Treatment with 1mg/kg/d of methylprednisolone vs steroid pulses was not associated with in-hospital mortality (13.5% vs 15.1%; OR, 0.880 [95% CI, 0.449-1.726]; p=0.710)

**Setting & Design**
Single center retrospective cohort study among 463 patients admitted to Hospital Puerta de Hierro-Majadahonda between March 4<sup>th</sup> and April 7th, 2020
- Treatment (n=396): patients treated with steroids
- Control (n=67): patients who did not receive steroids

**Outcome**
In hospital mortality

**Patient Population**
Adult patients diagnosed with COVID-19 pneumonia, complicated by ARDS and/or an hyperinflammatory syndrome

**Limitations**
Not yet peer-reviewed
- Retrospective study
- Confounding by indication: decision to prescribe steroids was at the discretion of the treating physician
  - Not part of local protocol
- Imbalance on baseline characteristics
- Small sample size

**Link**


**Question**
What risk factors are associated with long-term (>30 days) positive SARS-CoV-2 and viral shedding?

**Findings**
High dose corticosteroids (80mg/d solumedrol) associated with prolonged viral shedding (aHR, 0.67 [95%CI, 0.46-0.96]; p=0.031)
- Low-dose corticosteroids (40mg/d) were not associated with prolonged viral shedding (aHR, 0.72 [95%CI, 0.48-1.08]; p=0.11)

**Setting & Design**
Retrospective study of 206 patients in China to assess risk factors of long-term (>30d) COVID viral shedding

**Outcome**
Viral shedding
Prolonged (>30 days) positive SARS-CoV-2

**Patient Population**
206 patients with COVID-19

**Limitations**
Letter to the editor: methods and detailed results not presented

**Link**


**Question**
Are corticosteroids safe and efficacious in SARS-CoV-2?

**Findings**
Patients receiving early, low-dose methylprednisolone had faster improvement of clinical symptoms, including:
- Quicker resolution of hypoxia (8.2 days [IQR, 7.0-10.3] vs. 13.5 days [IQR, 10.3-16]; p<0.001)
- Quicker resolution of fever (2.06 days [±0.28] vs. 4.39 days [±0.70]; P=0.010)
- Greater resolution on chest imaging among patients receiving methylprednisolone
  - 43 (94.6%) of patients were discharged
  - Three (5.4%) patients died; 2/3 deaths were in methylprednisolone group

**Link**
### Setting & Design
Retrospective observational study among 46 patients with severe COVID-19 pneumonia hospitalized at the Union Hospital of Huazhong University of Science and Technology in Wuhan, China between January 20 and February 25, 2020
- Treatment (n=26): IV methylprednisolone 1-2mg/kg/d for 5-7d
  - Dose and duration determined by clinical manifestations, leucocyte count, lymphocyte count, inflammatory index, and lesion range
  - Untreated (n=20): no steroids.

### Outcome
Clinical symptoms (temperature, hypoxia) and chest CT imaging

### Patient Population
46 hospitalized patients with severe disease, defined as:
- Respiratory distress with respiratory rate ≥30 breaths/min
- Means oxygen saturation ≤ 93% or PaO2/FiO2 ≤ 300mmHg
- Age > 60 years, with complication of hypertension, diabetes, coronary disease, cancer, pulmonary heart disease, structural lung disease, or immunosuppression

### Limitations
Pre-print, not yet peer-reviewed
- Potential confounding by indication; unclear how treatment with corticosteroids was determined
- Not randomized
- Broad definition of severe disease may introduce variability
- Data on safety endpoints (other than death) not reported

### Link
[https://www.medrxiv.org/content/10.1101/2020.03.06.20032342v1](https://www.medrxiv.org/content/10.1101/2020.03.06.20032342v1)


### Question
What risk factors (including treatment with methylprednisolone) are associated with the development of ARDS and progression to death?

### Findings
Treatment with methylprednisolone may be beneficial for patients who develop ARDS
- 84 (42%) patients developed ARDS
  - Factors associated with development of ARDS: Age ≥65 years, fever ≥39 °C, hypertension, diabetes, neutrophilia, lymphocytopenia, CD3 and CD4 T-cell counts, LFTs, prealbumin, creatinine, glucose, LDH, low-density lipoprotein, serum ferritin, PT, and D-dimer
  - Compared with patients who did not have ARDS, patients who developed ARDS were less likely to be treated with antiviral therapy (-14.4% difference, 95% CI -26% to -2.9%; p= 0.005)
- 52% mortality in ARDS group
  - All patients who died had developed ARDS
  - Factors associated with death among patients with ARDS: older age, neutrophilia, LDH, D-dimer, IL-6
    - Fever ≥39 °C negatively associated with death
- Methylprednisolone: among patients with ARDS, treatment with methylprednisolone decreased risk of death (HR 0.38, 95% CI 0.2-0.72, p=0.003)
  - 46% receiving steroids died vs 61.8% without steroids
  - Patients who received steroids appeared to be sicker, as defined by a higher grade on Pneumonia Severity Index

### Setting & Design
Retrospective cohort study of 201 patients with confirmed COVID-19 pneumonia in Wuhan, China, admitted between December 25, 2019 and January 26
- Time to event: defined as the time from hospital admission to event (ARDS or death)
- Reported treatments:
  - 170 (85%) received antiviral treatment, including oseltamivir (134 [67%]), ganciclovir (81 [40%]), lopinavir/ritonavir (30 [15%]), and interferon alfa (22 [11%])
  - 196 (97%) received empiric antibiotics
  - 106 (52.7%) received antioxidant therapy, including glutathione and N-acetyl-L-cysteine
  - 62 (31%) received methylprednisolone
### Outcome
- Development of ARDS
- Death among patients who developed ARDS

### Patient Population
99 patients with RT-PCR confirmed SARS-CoV-2 admitted to Jinyintan Hospital in Wuhan, China
- 10 had previously been described in descriptive studies by Chen et al (11) and Huang et al (12)
- On chest imaging: 10 (5%) had unilateral infiltrates and 191 (95%) had bilateral infiltrates
- 66 (33%) patients with underlying chronic diseases

### Limitations
- Analyses:
  - Short follow-up: 13 (6.5%) patients were still hospitalized at time of writing, limiting analyses of outcome
  - Missing data for each variable were handled by complete case analysis, which may bias estimates
  - Incomplete testing for other viral, fungal, and/or bacterial respiratory infections
  - Confounding:
    - Confounding by indication in receipt of corticosteroids
    - Models do not appear to have adjusted for potential confounders

### Link


### Question
Are corticosteroids efficacious in patients with COVID-19?

### Findings
26 patients (84%) were discharged and 5 were still hospitalized at the end of follow-up
There was no significant difference in virologic or clinical outcomes associated with corticosteroid use
- Times to virus clearance: 14 days (IQR, 12–16 days; range, 7–26 days)
  - HR=1.26 (95% CI, 0.58–2.74; P = 0.55)
- Time to discharge: 18.5 days (IQR, 16–21 days)
  - HR=0.77 (95% CI, 0.33–1.78; P = 0.54)
- Time to clinical resolution of symptoms: 7 days (IQR, 5–10 days)
  - HR=0.86 (95% CI, 0.40–1.83; P = 0.70)

Unplanned analyses showed an association between HBV infection and prolonged virus clearance
- Mean difference: 10.6 days (95% CI, 6.2–15.1 days; P < 0.001).

### Setting & Design
Observational study among 31 patients with COVID-19 hospitalized at Second People’s Hospital of Wuhu or Yijishan Hospital in Wuhu, China between January 24 and February 24, 2020
- 11 patients received ≥ 1 dose corticosteroids during hospitalization
  - 40mg methylprednisolone administered 1-2 times per day, administered within 24 hours of admission for a median 5 days (IQR, 4.5–5.0 days)
  - Median time from illness onset to admission was four days (IQR, 2–6 days).
- All patients received inhaled lopinavir/ritonavir (median, 10 days [IQR, 8–11.5 days]) and interferon-α (median, 15 days [IQR, 10–17 days])
  - 5 patients received umifenovir (licensed for treatment of influenza in Russia & China)
  - 14 patients received prophylactic moxifloxacin for a median 6.5 days (IQR, 3.5–7.0 days)

### Outcome
- Primary outcome: time to virus clearance
- Secondary outcome: duration of clinical recovery, length of hospital stay

### Patient Population
31 hospitalized patients with mild COVID-19 in Wuhu, China

### Limitations
- Small sample size
  - Patient population: relatively young patients (median age, 39 years) with mild disease (no ARDS)
  - Observational study
### Descriptive Studies


**Question**
What are the clinical and epidemiologic features of COVID-19?

**Findings**
Report clinical characteristics and treatment course
- 19 received corticosteroids for 3-15 days (median, 5 days)
- At end of follow-up, 31 (31%) patients were discharged, 57 (58%) remained hospitalized, & 11 (11%) had died
- Oxygen requirements: 75 (76%)
  - 17 (17%) required mechanical ventilation for 4–22 days (median 9 days [IQR 7–19])
  - Four required invasive ventilation (still required ventilation at data cutoff)

**Setting & Design**
Retrospective descriptive study (case series) of all confirmed cases of SARS-CoV-2 in Wuhan Jinyintan Hospital, admitted between January 1 and January 20, 2020
- Clinical outcomes were followed up to January 25, 2020
- Reported treatments:
  - 75 (76%) received antiviral treatment, including oral oseltamivir (75 mg every 12 hours), IV ganciclovir (0.25 g every 12 hours), and lopinavir and ritonavir tablets (500 mg twice daily, orally)
    - Duration: 3–14 days (median 3 days [IQR 3–6])
  - 70 (71%) received antibiotics: 25 (25%) patients received a single antibiotic and 45 (45%) patients received combination therapy
    - Duration: 3–17 days (median 5 days [IQR 3–7])
  - 19 (19%) received glucocorticoids (methylprednisolone sodium succinate, methylprednisolone, and dexamethasone)
    - Duration: 3–15 days (median 5 [3–7])

**Outcome**
Epidemiology and clinical characteristics of COVID-19.

**Patient Population**
99 patients with RT-PCR confirmed SARS-CoV-2 admitted to Jinyintan Hospital in Wuhan, China
- 49 (49%) had a history of exposure to the Huanan seafood market
  - 47 had a history of long-term exposure
- 50 (51%) patients with underlying chronic diseases
- 33 (33%) presented with organ function damage, including 17 (17%) with ARDS and eight (8%) with acute respiratory injury

**Limitations**
Descriptive studies are hypothesis generating and cannot establish causal relationships
- Short follow-up: 58% of patients were still hospitalized at the time of analyses, limiting outcome data
- Outcomes were not stratified by treatment: Cannot compare cases

**Link**


**Question**
How do the clinical features of COVID-19 differ between intensive care unit (ICU) and non-ICU patients?

**Findings**
Report clinical characteristics and treatment course
- 9 received corticosteroids
- At the time of writing, 28 (68%) patients were discharged, 7 (27%) remained in the hospital, and 6 (15%) had died
- Oxygen requirements: 75 (76%)
  - 17 (17%) required mechanical ventilation for 4–22 days (median 9 days [IQR 7–19])
- Compared with non-ICU patients, ICU patients had higher levels of cytokines (IL2, IL7, IL10, GSCF, IP10, MCP1, MIP1A, and TNF-alpha)

**Setting & Design**
Retrospective descriptive study of all confirmed cases of SARS-CoV-2 in Wuhan Jinyintan Hospital, admitted between January 1 and January 20, 2020
- Clinical outcomes were followed up to January 25, 2020
- Reported treatments:
  - Antiviral treatment: 75 (76%) patients received antiviral treatment
    - Duration: 3–14 days (median 3 days [IQR 3–6])
  - Antibiotics: 70 (71%) patients received antibiotics
    - Duration: 3–17 days (median 5 days [IQR 3–7])
  - Glucocorticoids: 19 (19%) patients received glucocorticoids
    - Duration: 3–15 days (median 5 [3–7])

**Limitations**
Descriptive studies are hypothesis generating and cannot establish causal relationships
- Short follow-up: 58% of patients were still hospitalized at the time of analyses, limiting outcome data
- Outcomes were not stratified by treatment: Cannot compare cases

**Link**
- Nine (22%) patients were given systemic corticosteroids
  - 6 (67%) were ICU patients:
    - 4 (44%) died, compared to 2 (6.3%) patients who did not receive corticosteroids
  - All patients required some degree of oxygen support
    - 4 (10%) required invasive mechanical ventilation

**Setting & Design**
Prospective descriptive study of confirmed SARS-CoV-2 cases in Wuhan, China, admitted from December 31, 2019 to January 2, 2020
- Clinical outcomes were followed up to January 2, 2020
- Reported treatments:
  - 38 (93%) received antiviral treatment, oseltamivir (orally 75 mg twice daily)
  - 41 (100%) received empiric antibiotics
  - 9 (22%) received methylprednisolone 40–120 mg per day for severe community-acquired

**Outcome**
Epidemiology and clinical characteristics of COVID-19.

**Patient Population**
Of 59 suspected cases, 41 patients with RT-PCR confirmed SARS-CoV-2
- 27 (66%) had a history of exposure to the Huanan seafood market
- All patients were diagnosed with pneumonia
- 13 (32%) were admitted to the ICU for increased oxygen support

**Limitations**
Descriptive studies are hypothesis generating and cannot establish causal relationships
- Timing of administration of corticosteroids in treatment course is unknown
- Short follow-up: 27% of patients were still hospitalized at the time of analyses, limiting outcome data

**Link**


**Question**
Can steroids reverse severe COVID-19-induced cytokine storm?

**Findings**
All patients experienced clinical improvement
- None needed intubation
- 4 cleared the virus by time of discharge (median 17.2d, range 14-23d)

**Setting & Design**
Case series of 6 patients with severe COVID-19 pneumonia with ARDS and laboratory evidence of hyper-inflammatory syndrome admitted to “Sotiria” Chest Hospital, Athens, Greece between March 19th and April 24th 2020
- Theory that COVID-19 associated hyper-inflammatory syndrome (CAHS) could be similar to secondary HLH which is often triggered by viral infections and early high dose corticosteroids in an important therapy for secondary HLH.
  - Treatment with methylprednisolone 125mg daily
  - Received azithromycin, hydroxychloroquine, beta-lactam, prophylaxis with low-molecular-weight heparin and oxygen therapy
    - Four patients did not receive hydroxychloroquine due to laboratory confirmed glucose-6-phosphate dehydrogenase deficiency (G6PD)
  - One patient tested positive for influenza and received oseltamivir

**Outcome**
Clinical course

**Patient Population**
Patients who developed ARDS (PaO2/FiO2 < 300mmHg) either at admission or shortly after

**Limitations**
Small case series with poor generalizability
- 4/6 patients had G6PD deficiency
- Unclear why 5/11 patients with ARDS were not included

**Link**

**Systematic Reviews & Meta-analyses**


**Question**
What is the role of corticosteroids in coronavirus infections?
### Findings

Severely ill patients were more likely to require corticosteroids therapy (RR, 1.56 [95% CI, 1.28–1.90]; *P* < 0.001)
- Similar results in subgroup analysis of patients with SARS-CoV-2 (RR, 2.36 [95% CI, 1.31–4.28]; *P* = 0.004) & SARS-CoV (RR, 1.46, [95% CI, 1.18–1.80]; *P* < 0.001)

Higher mortality among patients who received corticosteroids (RR, 2.11 [95% CI, 1.13–3.94]; *P* = 0.019)
- Association between mortality and steroid use was not stable in sensitivity analysis

Length of stay was longer in the corticosteroid group (*p* < 0.001)
- Patients treated w/ corticosteroids were more likely to have adverse reactions
  - Bacterial infection: RR=2.08 (95% CI, 1.54–2.81; *P* < 0.001)
  - Hypokalemia: RR=2.21 (95% CI, 1.07–4.55; *P* = 0.032)

### Setting & Design

Systematic review and meta-analysis of corticosteroids in coronavirus infection between January 2002 and March 15, 2020
- Studies (n=15): subjects with SARS-CoV (11 studies), MERS-CoV (2 studies), or SARS-CoV-2 (2 studies)
  - 9 studies assessed mortality

### Outcome

- Mortality
- Length of stay
- Adverse reactions

### Patient Population

Adult patients (n=5,270) dichotomized into corticosteroid use (experimental) or no corticosteroid use (control)

### Limitations

Design
- Most studies were retrospective studies
- No uniform standard for the time and dosage of steroids
- Significant heterogeneity across studies

Analyses
- Confounding of effect of corticosteroids by use of other therapies (e.g. antivirals)
- Confounding by indication: sicker patients were more likely to receive steroids
- Data on adverse reactions were based on only 2 studies

### Link


What is the impact of corticosteroids in COVID-19 and related severe acute respiratory illnesses?

- In ARDS corticosteroids may reduce mortality based on one small COVID 19 cohort study and 7 non-COVID-19
- For non-ARDS severe COVID-19, two observational studies with very low-evidence of increased mortality w/ corticosteroids
- Observational data from SARS and MERS with low-quality evidence of small or no mortality benefit

- Included randomized controlled trials, cohort studies, and case–control studies that compared corticosteroids versus no corticosteroids

Mortality benefit

Patients with COVID-19, SARS or MERS or viral pneumonia

- Small number of studies with predominantly low quality of evidence
- Heterogeneity in analyses


<table>
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<tr>
<th>Question</th>
<th>Commentary on the use of hydroxychloroquine and chloroquine in SARS-CoV-2.</th>
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| Findings | Chinese Thoracic Society developed expert consensus statement on use of corticosteroids in COVID-19, with the following basic principles:  
  - The benefits and harms should be carefully weighed before initiating corticosteroids  
  - Corticosteroids should be used prudently in critically ill patients with 2019-nCoV pneumonia  
  - Cautious use of steroids among patients with hypoxemia due to underlying diseases or who regularly use corticosteroids for chronic diseases  
  - Low to moderate dose (≤0.5–1 mg/kg per day methylprednisolone or equivalent) & short duration (≤7 days)  
Authors acknowledge potential risk of high dose-steroids; however, inflammation and cytokine-related lung injury in critically ill patients may result in rapidly progressive pneumonia |
| Setting & Design | Review & commentary on the use of hydroxychloroquine and chloroquine in SARS-CoV-2, based on their experience with 2000 dosages of hydroxychloroquine during the past 5 years  
  - Note that most studies are observational |
| Outcome | N/A |
| Patient Population | N/A |
| Limitations | Study is a review  
  - Did not perform meta-analyses to support arguments |

**Evidence in SARS-CoV-1 & MERS-CoV**


<table>
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<tr>
<th>Question</th>
<th>Is corticosteroid therapy associated with mortality and MERS coronavirus RNA clearance in critically ill patients with MERS?</th>
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| Findings | 151 (49%) received corticosteroids (median initiation following admission to ICU, 3 days [IQR, 1-7 days])  
Corticosteroid therapy was not associated with a difference in mortality, after adjustment for time-varying confounders  
  - Higher 90-day crude mortality associated with corticosteroids: 112 (74.2%) vs. 91 (57.6%; P = 0.002)  
  - No difference in adjusted analyses: adjusted odds ratio, 0.75 (95% confidence interval, 0.52–1.07; P = 0.12)  
Corticosteroids were associated with a longer median (IQR) ICU and hospital length of stay  
  - ICU length of stay: 12.5 days (8.0–23.0 days) versus 7.0 (5.0–13.0 days; P<0.0001)  
  - Hospital length of stay: 21.0 days (13.0–38.0 days) versus 15.0 days (8.0–30.0 days; P = 0.0006)  
Corticosteroid use was associated with delay in MERS coronavirus RNA clearance (adjusted HR, 0.35; 95% CI, 0.17–0.72; P = 0.005) |
| Setting & Design | Multicenter, retrospective cohort study across 14 tertiary care hospitals in Saudi Arabia  
  - Exposure: system corticosteroid therapy  
    - Preparations converted to hydrocortisone-equivalent doses (methylprednisolone 1:5, dexamethasone 1:25, prednisolone 1:4) |
| Outcome |  
  - Primary outcome: 90-day all-cause mortality  
  - Secondary outcome: Length of stay in the ICU and hospital  
  - Time to MERS-CoV RNA clearance in respiratory secretions: time from ICU admission until the test was negative on two occasions, without a positive test afterward  
    - Only performed among patients who had ≥1 follow-up RT-PCR after the diagnostic test |
| Patient Population | All patients (309) with MERS admitted to the ICU between September 2012 and October 2015  
  - Exclusion Criteria: receiving chronic corticosteroid therapy before the onset of critical illness |
**Limitations**
- Confounding: unmeasured confounders & confounding by indication
- Not all patients received follow-up MERS-CoV RNA testing

**Link**


**Question**
Are corticosteroids associated with morbidity & mortality benefit in patients with SARS-CoV-1?

**Findings**
- Inconclusive evidence of benefit in SARS, with some evidence of adverse events
  - SARS-infected patient: 25/29 were inconclusive
    - 4 were classified as causing possible harm
      - Evidence of avascular necrosis and steroid-induced psychosis in SARS patients
  - ARDS: 2/3 trial indicated that high-dose methylprednisolone for 2 days was not effective for early ARDS
    - One small RCT of lower dose methylprednisolone (2 mg/kg per day), tapered after 2 weeks, found possible evidence of ARDS improvement

**Setting & Design**
- Systematic review designed to summarize available evidence on the effects of ribavirin, lopinavir and ritonavir, corticosteroids, type I IFN, intravenous immunoglobulin (IVIG), or convalescent plasma in SARS and ARDS, regarding:
  - In vivo studies of ≥10 patients treated for SARS, including randomized controlled trials (RCT), prospective uncontrolled study design, retrospective cohort design, case-control design, case series
  - Studies of ARDS or acute lung injury among ≥20 patients, including RCT or systematic review

**Outcome**
1. Mortality or morbidity in SARS patients
2. Effects on ARDS in adult patients

**Patient Population**
- In vitro evidence: 15 studies
- Clinical evidence of SARS treatment in humans: 54 studies (37 in English, 17 in Chinese)
- ARDS: 3 studies

**Limitations**
- Wide variance in treatment regimens
- Studies were largely inconclusive

**Link**

**Evidence in Other Respiratory Illnesses**


**Question**
Assess effectiveness and potential adverse effects of corticosteroids as adjunctive therapy in the treatment of influenza

**Findings**
- Corticosteroid therapy was associated with increased mortality
  - Odds ratio (OR): 3.90 (95% CI, 2.31 to 6.60; I² = 68%; 15 studies)
  - Stratified analysis of studies reporting adjusted estimates: OR 2.23 (95% CI 1.54 to 3.24; I² = 0%; 5 studies)
  - Pooled analysis of six studies reporting adjusted hazard ratios (HRs): 1.49 (95% CI 1.09 to 2.02; I² = 69%)
  - Increased odds of hospital-acquired infection related to corticosteroid therapy were found on pooled analysis of seven studies
    - Pooled OR 2.74 (95% CI 1.51 to 4.95; I² = 90%)
    - Low certainty grade: all were unadjusted estimates
  - Currently available evidence is insufficient to determine the effectiveness of corticosteroids for people with influenza

**Setting & Design**
- Meta-analysis of randomized controlled trials (RCTs), quasi-RCTs, and observational studies that compared corticosteroid treatment with no corticosteroid treatment for influenza or influenza-like illness
  - Pooled estimates of effect using a random-effects model
  - Certainty of the evidence assessed using the GRADE framework

**Outcome**
1. Mortality
2. Secondary infection

**Patient Population**
- Studies comparing additional steroid treatment with no additional steroid treatment in individuals with influenza
  - 30 studies with 99,224 individuals
Limitations

- Majority of evidence was from observational studies
- Only one RCT with 24 patients with confirmed influenza infection
- Differences in measurement & reporting across studies:
  - Inconsistent reporting of important variables: time to hospitalization; use and timing of antiviral drugs and antibiotics; type, dose, timing, and duration of corticosteroid therapy
  - Indications for corticosteroid therapy were not fully specified in many of the studies
    - Confounding by indication in many studies: association between corticosteroids and the presence of potentially confounding factors, such as disease severity and underlying illnesses

**Link**  


**Question**  
What is the effectiveness of dexamethasone in ARDS?

**Findings**

- Dexamethasone was associated with a greater mean number of ventilator-free days: 12.3 days (SD, 9.9) versus 7.5 days (SD, 9.0) (between-groups difference, 4.8 days [95% CI, 2.57–7.03]; p<0·0001)
  - Among extubated patients, 12 (8.6%) patients in the dexamethasone group versus 7 (5.1%) in the control group required reintubation within the 28-day period after randomization
    - Number of deaths among patients with extubation failure were similar between groups (3 [25%] vs. 2 [29%])
  - Mean duration of mechanical ventilation was 24 days (SD, 9) in the dexamethasone group versus 20 days (SD, 12) days in the control group
  - No differences in ICU mortality associated with duration of dexamethasone treatment
  - Decreased mortality at 60 days after randomization among patients in dexamethasone group (n=29 [21%]) compared to control (n=50 [36%]; p=0.0047)
  - No difference in adverse events

**Setting & Design**

- Multicenter randomized control trial among 277 patients with ARDS admitted across 17 intensive care units in teaching hospitals across Spain between March 28, 2013, and Dec 31, 2018
- Onset of ARDS defined as the day and time in which the patient first met moderate-to-severe ARDS criteria
- Random assignment via block randomization
  - Treatment (n=139): IV dexamethasone, 20 mg once daily from day 1 to day 5, followed by 10 mg once daily from day 6 to day 10
    - Received the first dose immediately after being randomly assigned (no later than 30 h after ARDS onset
  - Control (n=138): continued routine intensive care
    - Patients with non-resolving ARDS due to a corticosteroid-sensitive lung condition could receive corticosteroids

**Outcome**

- Primary outcome: Number of ventilator-free days at 28 days after randomization
  - Ventilator-free defines as: >48 hours without reintubation in patients who survived 28 days after randomization
  - Ventilator-free days recorded as zero in patients ventilated for 28 days or more or who died before 28 days (irrespective of intubation status)
- Secondary outcome: Death from any cause 60 days after randomization

**Patient Population**

- Adult patients aged ≥18 years with acute-onset ARDS requiring intubation and mechanically ventilation
- ARDS defined as moderate-to-severe by the American-European Consensus Conference criteria for ARDS or by the Berlin criteria
- Exclusion criteria: pregnancy or active lactation, brain death, terminal-stage cancer or other disease, a decision to do-not-resuscitate, treatment with corticosteroids or immunosuppressive drugs, enrollment in another experimental treatment protocol, severe chronic obstructive pulmonary disease, or congestive heart failure

**Limitations**

- Small sample size
  - Trial was stopped following recommendations by the data and safety monitoring board due to low enrolment numbers

**Generalizability**

Enrolled 27% of eligible patients
Excluded patients with major pre-existing comorbidities
Excluded patients with corticosteroid-sensitive pathologies who would be expected to have a higher likelihood of benefiting from steroid
Variability and confounding across centers
Treatment with corticosteroids in randomized control patients

References

Link: https://pubmed.ncbi.nlm.nih.gov/32043986/