Table 6a. Systemic Corticosteroids: Selected Clinical Data

Last Updated: May 31, 2022

The clinical trials described in this table do not represent all the trials that the Panel reviewed while developing the recommendations for systemic corticosteroids. The studies summarized below are those that have had the greatest impact on the Panel’s recommendations. Unless stated otherwise, the clinical trials listed below only included participants aged ≥18 years.

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<tr>
<th>Methods</th>
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<tr>
<td><strong>RECOVERY: Open-Label RCT of Dexamethasone in Hospitalized Patients With COVID-19 in the United Kingdom</strong></td>
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<tr>
<td><strong>Key Inclusion Criterion:</strong></td>
<td><strong>Participant Characteristics:</strong></td>
<td><strong>Key Limitations:</strong></td>
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<tr>
<td>• Hospitalized with suspected or</td>
<td>• Mean age 66 years; 64% men; 73% White</td>
<td>• Open-label study</td>
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<td>laboratory-confirmed SARS-CoV-2 infection</td>
<td>• 56% had ≥1 comorbidity; 24% with DM</td>
<td>• Published data did not include results for key secondary endpoints (e.g., cause-specific</td>
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<tr>
<td><strong>Key Exclusion Criteria:</strong></td>
<td>• 89% had laboratory-confirmed SARS-CoV-2 infection</td>
<td>mortality, need for renal replacement, AEs, and key subgroups (e.g., patients with</td>
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<td>• Physician determination that risks of</td>
<td>• Median duration of DEX therapy: 7 days</td>
<td>comorbidities).</td>
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<td>participation were too great based on</td>
<td>• At randomization:</td>
<td>• Patients who required supplemental oxygen (but not MV) had variable severity of illness.</td>
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<td>patient's medical history</td>
<td>• 16% received MV or ECMO</td>
<td>It is unclear whether all patients in this group benefited from DEX or whether benefit</td>
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<td>• An indication for corticosteroid therapy</td>
<td>• 60% required supplemental oxygen but not MV</td>
<td>is restricted to those requiring higher levels of supplemental oxygen.</td>
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<td>outside of the study</td>
<td>• 24% required no supplemental oxygen</td>
<td>• Patients aged &gt;80 years were preferentially assigned to receive supplemental oxygen therapy</td>
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<td><strong>Interventions:</strong></td>
<td>• Received RDV: &lt;1% in both arms</td>
<td>(and not MV).</td>
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<td>• DEX 6 mg IV or PO once daily plus SOC</td>
<td>• Received tocilizumab or sarilumab: 2% in DEX arm vs. 3% in SOC arm</td>
<td>• High mortality in this study may limit the generalizability of results to populations with</td>
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<td>for up to 10 days or until discharge (n =</td>
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<td>a lower baseline mortality.</td>
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<td>2,104)</td>
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<td>• SOC alone (n = 4,321)</td>
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<td><strong>Primary Endpoint:</strong></td>
<td><strong>Primary Outcome:</strong></td>
<td><strong>Interpretation:</strong></td>
</tr>
<tr>
<td>• All-cause mortality at 28 days</td>
<td>• All-cause mortality at 28 days</td>
<td>• In hospitalized patients with severe COVID-19 who required supplemental oxygen, DEX</td>
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<td></td>
<td>• All patients: 23% in DEX arm vs. 26% in SOC arm (age-adjusted rate</td>
<td>reduced mortality at 28 days. The greatest benefit was seen in those receiving MV at</td>
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<td>ratio 0.83; 95% CI, 0.75–0.93; ( P &lt; 0.001 )</td>
<td>randomization.</td>
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<td>• Patients who required MV or ECMO at randomization: 29% in DEX arm</td>
<td>• There was no survival benefit for DEX in patients who did not require supplemental oxygen</td>
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<td>vs. 41% in SOC arm (rate ratio 0.64; 95% CI, 0.51–0.81)</td>
<td>at randomization.</td>
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<td>• Patients who required supplemental oxygen but not MV at</td>
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<td>randomization: 23% in DEX arm vs. 26% in SOC arm (rate ratio 0.82;</td>
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<td>95% CI, 0.72–0.94)</td>
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<td></td>
<td>• Patients who did not require supplemental oxygen at</td>
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CoDEX: Open-Label RCT of Dexamethasone in Patients With Moderate or Severe ARDS and COVID-19 in Brazil

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<thead>
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</table>
| **Key Inclusion Criteria:**<br>• Confirmed or suspected SARS-CoV-2 infection<br>• Received MV within 48 hours of meeting criteria for moderate to severe ARDS (PaO₂/FiO₂ ≤200 mm Hg)<br>**Key Exclusion Criteria:**<br>• Received immunosuppressive drugs in past 21 days<br>• Death expected within 24 hours<br>**Interventions:**<br>• DEX 20 mg IV once daily for 5 days, then DEX 10 mg IV once daily for 5 days or until ICU discharge (n = 151)<br>• SOC alone (n = 148)<br>**Primary Endpoint:**<br>• Number of days alive and free from MV by Day 28<br>**Key Secondary Endpoints:**<br>• All-cause mortality by Day 28<br>• Number of ICU-free days by Day 28<br>• Duration of MV by Day 28<br>• Score on 6-point OS at Day 15<br>• SOFA score at Day 7<br>randomization: 18% in DEX arm vs. 14% in SOC arm (rate ratio 1.19, 95% CI, 0.92–1.55)<br>**Participant Characteristics:**<br>• Mean age 61 years; 63% men<br>• Comorbidities:<br>  • Obesity: 31% in DEX arm vs. 24% in SOC arm<br>  • DM: 38% in DEX arm vs. 47% in SOC arm<br>  • Vasopressor use: 66% in DEX arm vs. 68% in SOC arm<br>  • Mean PaO₂/FiO₂: 131 mm Hg in DEX arm vs. 133 mm Hg in SOC arm<br>  • Median duration of DEX therapy: 10 days<br>  • No patients received RDV or tocilizumab<br>  • 35% in SOC arm received corticosteroids for indications such as bronchospasm or septic shock<br>**Primary Outcome:**<br>• Mean number of days alive and free from MV by Day 28: 7 in DEX arm vs. 4 in SOC arm (P = 0.04)<br>**Secondary Outcomes:**<br>• No differences between arms in all-cause mortality (56% vs. 62%), number of ICU-free days, duration of MV, or score on 6-point OS<br>• Mean SOFA score at Day 7: 6.1 in DEX arm vs. 7.5 in SOC arm (P = 0.004)<br>**Other Outcome:**<br>• Post hoc analysis of probability of death or MV by Day 15: 68% in DEX arm vs. 80% in SOC arm (OR 0.46)<br>**Key Limitations:**<br>• Open-label study<br>• Underpowered; enrollment stopped after release of data from the RECOVERY trial.<br>• Patients discharged before 28 days were not followed for rehospitalization or mortality.<br>• High mortality in this study may limit the generalizability of results to populations with a lower baseline mortality.<br>• More than one-third of those randomized to receive SOC also received corticosteroids.<br>**Interpretation:**<br>• Compared with SOC alone, DEX increased the number of days alive and free of MV over 28 days in patients with COVID-19 and moderate to severe ARDS.
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<tr>
<td><strong>Observational Cohort Study of Dexamethasone in Hospitalized Patients With COVID-19 Who Were Not on Intensive Respiratory Support in the United States</strong>&lt;sup&gt;3&lt;/sup&gt;</td>
<td><strong>Key Inclusion Criterion:</strong>&lt;br&gt;• Within 14 days of a positive test result for SARS-CoV-2 infection</td>
<td><strong>Key Limitations:</strong>&lt;br&gt;• Retrospective observational study&lt;br&gt;• Because nearly all patients on MV or HFNC oxygen received DEX, analysis was restricted to patients who did not receive IRS (i.e., those who received no supplemental oxygen or only low-flow nasal cannula oxygen).&lt;br&gt;• Differences between the arms in other therapies received</td>
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<td><strong>Key Exclusion Criteria:</strong>&lt;br&gt;• Recent receipt of corticosteroids&lt;br&gt;• Receipt of IRS (defined as HFNC oxygen, NIV, or MV) within 48 hours&lt;br&gt;• Hospital LOS of &lt;48 hours</td>
<td><strong>Participant Characteristics:</strong>&lt;br&gt;• Mean age 71 years; 95% men; 27% Black, 55% White&lt;br&gt;• 77% did not receive IRS within 48 hours&lt;br&gt;• 83% admitted within 1 day after positive SARS-CoV-2 test result&lt;br&gt;• Median duration of DEX for patients who did not receive IRS: 5 days for patients who were not on supplemental oxygen at baseline vs. 6 days for patients on low-flow nasal cannula oxygen&lt;br&gt;• Received RDV: 43% of those who received DEX vs. 13% of those who did not&lt;br&gt;• Received anticoagulants: 46% of those who received DEX vs. 10% of those who did not</td>
<td><strong>Interpretation:</strong>&lt;br&gt;• In hospitalized patients with COVID-19, the use of DEX was not associated with a mortality benefit among those who received low-flow nasal cannula oxygen during the first 48 hours after admission, but it was associated with increased mortality among those who received no supplemental oxygen during the first 48 hours after admission.</td>
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<td><strong>Interventions:</strong>&lt;br&gt;• Corticosteroids (95% of patients received DEX) administered within 48 hours of admission (n = 7,507)&lt;br&gt;• No corticosteroids administered (n = 7,433)</td>
<td><strong>Primary Endpoint:</strong>&lt;br&gt;• All-cause mortality at 90 days</td>
<td><strong>Primary Outcome:</strong>&lt;br&gt;• Risk of all-cause mortality at 90 days was higher in those who received DEX:&lt;br&gt;• For combination of those not on supplemental oxygen and those on low-flow nasal cannula oxygen: HR 1.59; 95% CI, 1.39–1.81&lt;br&gt;• For those not on supplemental oxygen: HR 1.76; 95% CI, 1.47–2.12&lt;br&gt;• For those on low-flow nasal cannula oxygen: HR 1.08; 95% CI, 0.86–1.36</td>
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### COVID STEROID 2: Blinded RCT of Dexamethasone 12 mg Versus 6 mg in Hospitalized Adults With COVID-19 and Severe Hypoxemia in Denmark, India, Sweden, and Switzerland

#### Key Inclusion Criteria:
- Confirmed SARS-CoV-2 infection
- Requiring oxygen ≥10 L/min, NIV, CPAP, or MV

#### Key Exclusion Criteria:
- Treated with DEX >6 mg (or equivalent)
- Treated with a corticosteroid within past 5 days
- Invasive fungal infection or active TB

#### Interventions:
- DEX 12 mg IV once daily for up to 10 days ($n = 497$)
- DEX 6 mg IV once daily for up to 10 days ($n = 485$)

#### Primary Endpoint:
- Number of days alive without life support (MV, circulatory support, or kidney replacement therapy) at 28 days

#### Key Secondary Endpoints:
- Number of days alive without life support at 90 days
- Number of days alive and out of hospital at 90 days
- Mortality at 90 days
- Mortality at 28 days
- SAEs at 28 days

#### Participant Characteristics:
- Median age 65 years; 31% women
- DM: 27% in 12 mg arm vs. 34% in 6 mg arm
- Median time from symptom onset to hospitalization: 7 days in both arms
- Received ICU care: 78% in 12 mg arm vs. 81% in 6 mg arm
- Oxygen requirements:
  - 54% on oxygen via nasal cannula or face mask (median flow rate 23 L/min)
  - 25% on NIV
  - 21% on MV
- 63% received RDV; 12% received IL-6 inhibitors or JAK inhibitors
- Median duration of DEX treatment: 7 days in both arms

#### Primary Outcome:
- Median number of days alive without life support: 22.0 in 12 mg arm vs. 20.5 in 6 mg arm (adjusted mean difference 1.3 days; 95% CI, 0.0–2.6; $P = 0.07$)
- 63.9% Bayesian probability of clinically important benefit and 0.3% Bayesian probability of clinically important harm for DEX 12 mg

#### Secondary Outcomes:
- At 90 days:
  - Median number of days alive without life support: 84 in 12 mg arm vs. 80 in 6 mg arm ($P = 0.15$)
  - Median number of days alive and out of hospital: 62 in 12 mg arm vs. 48 in 6 mg arm ($P = 0.09$)
  - Mortality: 32% in 12 mg arm vs. 38% in 6 mg arm (adjusted relative risk 0.87; 99% CI, 0.70–1.07; $P = 0.09$)

#### Key Limitation:
- The randomized intervention period was <10 days in some patients because the trial allowed up to 4 days of DEX before enrollment.

#### Interpretation:
- Among patients with COVID-19 and severe hypoxemia, the use of DEX 12 mg once daily did not result in more days alive without life support at 28 days than DEX 6 mg once daily.
**COVID STEROID 2: Blinded RCT of Dexamethasone 12 mg Versus 6 mg in Hospitalized Adults With COVID-19 and Severe Hypoxemia in Denmark, India, Sweden, and Switzerland**

At 28 days:
- **Mortality**: 27% in 12 mg arm vs. 32% in 6 mg arm (adjusted relative risk 0.86; 99% CI, 0.68–1.08; \( P = 0.10 \))
- **SAEs**, including septic shock and invasive fungal infections: 11% in 12 mg arm vs. 13% in 6 mg arm (adjusted relative risk 0.83; 99% CI, 0.54–1.29; \( P = 0.27 \))

**CAPE COVID: Double-Blind RCT of Hydrocortisone Among Critically Ill Patients With COVID-19 in France**

**Key Inclusion Criteria:**
- Laboratory-confirmed SARS-CoV-2 infection or radiographically suspected COVID-19 with \( \geq 1 \) of the following:
  - MV with PEEP \( \geq 5 \) cm H\(_2\)O
  - \( \text{PaO}_2/\text{FiO}_2 \) <300 mm Hg and \( \text{FiO}_2 \) \( \geq 50\% \) on HFNC
  - \( \text{PaO}_2/\text{FiO}_2 \) <300 mm Hg on reservoir mask oxygen
  - Pulmonary severity index >130

**Key Exclusion Criteria:**
- Septic shock
- Do-not-intubate orders

**Interventions:**
- Continuous IV infusion of hydrocortisone 200 mg per day for 7 days, then 100 mg per day for 4 days, then 50 mg per day for 3 days. If patient improved by Day 4, then IV infusion of hydrocortisone 200 mg per day for 4 days, then 100 mg per day for 2 days, then 50 mg per day for 2 days (\( n = 76 \))
- Placebo (\( n = 73 \))

**Participant Characteristics:**
- Mean age 62 years; 70% men; median BMI 28
- 96% had laboratory-confirmed SARS-CoV-2 infection
- Median symptom duration: 9–10 days
- Required MV at baseline: 81%
- Received vasopressors: 24% in hydrocortisone arm vs. 18% in placebo arm
- Received RDV or tocilizumab: <5%
- Median duration of treatment with study drug: 11 days in hydrocortisone arm vs. 13 days in placebo arm (\( P = 0.25 \))

**Primary Outcome:**
- Treatment failure by Day 21: 42% in hydrocortisone arm vs. 51% in placebo arm (\( P = 0.29 \))

**Secondary Outcomes:**
- No difference between arms in need for intubation or prone positioning (too few patients received ECMO or inhaled nitric oxide for comparisons)
- Among patients who did not require MV at baseline, 50% in hydrocortisone arm vs. 75% in placebo arm required subsequent MV
- No difference between arms in proportion of patients with nosocomial infection by Day 28

**Key Limitations:**
- Underpowered; enrollment stopped after release of data from the RECOVERY trial, resulting in limited power to detect differences between arms.
- Limited information about comorbidities

**Interpretation:**
- The use of hydrocortisone did not reduce the proportion of patients with COVID-19 and acute respiratory failure who experienced treatment failure by Day 21.
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<td><strong>CAPE COVID</strong>: Double-Blind RCT of Hydrocortisone Among Critically Ill Patients With COVID-19 in France, continued</td>
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<tr>
<td><strong>Primary Endpoint:</strong></td>
<td>• No difference between arms in clinical status on Day 21, but 15% died in hydrocortisone arm vs. 27% in placebo arm ((P = 0.06))</td>
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<tr>
<td>• Treatment failure (death or dependency on MV or high-flow oxygen) by Day 21</td>
<td>• Discharged from ICU by Day 21: 57% in hydrocortisone arm vs. 44% in placebo arm; 23% in both arms still required MV</td>
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<td><strong>Key Secondary Endpoints:</strong></td>
<td>• Discharged from ICU by Day 21: 57% in hydrocortisone arm vs. 44% in placebo arm; 23% in both arms still required MV</td>
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<td>• Need for MV, prone positioning, ECMO, or inhaled nitric oxide</td>
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<td>• Nosocomial infection by Day 28</td>
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<tr>
<td>• Clinical status on Day 21, as measured by a 5-item scale:</td>
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<tr>
<td>• Death</td>
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<td>• In ICU and on MV</td>
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<tr>
<td>• Required high-flow oxygen therapy</td>
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<tr>
<td>• Required low-flow oxygen therapy</td>
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<td>• Discharged from ICU</td>
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| **REMAP-CAP**: Randomized, Open-Label, Adaptive Trial of Hydrocortisone in Patients With Severe COVID-19 | | |
| **Key Inclusion Criteria:** | | |
| • Presumed or laboratory-confirmed SARS-CoV-2 infection | | |
| • ICU admission for respiratory or cardiovascular support | | |
| **Key Exclusion Criteria:** | | |
| • Presumed imminent death | | |
| • Systemic corticosteroid use | | |
| • >36 hours since ICU admission | | |
| **Interventions:** | | |
| • Hydrocortisone 50 mg IV every 6 hours for 7 days \((n = 137)\) | | |
| • Shock-dependent hydrocortisone 50 mg IV every 6 hours for duration of shock for up to 28 days \((n = 146)\) | | |
| • No hydrocortisone \((n = 101)\) | | |

| **Participant Characteristics:** | | |
| • Mean age 60 years; 71% men; 53% White | | |
| • Mean BMI 29.7–30.9 | | |
| • 50% to 64% required MV | | |

| **Primary Outcome:** | | |
| • No difference between arms in median number of organ support-free days at Day 21 \((0 \text{ in each arm})\) | | |
| • Median adjusted ORs for primary outcome for hydrocortisone arms compared to no hydrocortisone arm: | | |
| • OR 1.43 (95% CrI, 0.91–2.27) with 93% Bayesian probability of superiority for fixed-dose hydrocortisone arm | | |
| • OR 1.22 (95% CrI, 0.76–1.94) with 80% Bayesian probability of superiority for shock-dependent hydrocortisone arm | | |

| **Key Secondary Outcome:** | | |
| • No difference between arms in in-hospital mortality (30% in | | |

| **Key Limitations:** | | |
| • Open-label study | | |
| • Enrollment stopped after release of data from the RECOVERY trial. | | |

| **Interpretation:** | | |
| • The use of hydrocortisone did not increase the median number of support-free days in either the fixed-dose or the shock-dependent hydrocortisone arms, although early termination limited the study’s power to detect differences between the study arms. | | |
## REMAP-CAP: Randomized, Open-Label, Adaptive Trial of Hydrocortisone in Patients With Severe COVID-19

**Primary Endpoint:**
- Number of days free from respiratory and cardiovascular support by Day 21

**Key Secondary Endpoint:**
- In-hospital mortality

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<th>固定剂量氢化可的松组 vs. 吸收依赖氢化可的松组 vs. 无氢化可的松组</th>
<th>26% vs. 33%</th>
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## Single-Blind RCT of Methylprednisolone in Hospitalized Patients With COVID-19 Pneumonia in China

**Key Inclusion Criteria:**
- Laboratory-confirmed SARS-CoV-2 infection
- Pneumonia confirmed by chest CT scan
- Hospitalized on general ward for <72 hours

**Key Exclusion Criteria:**
- Severe immunosuppression
- Corticosteroid use for other diseases

**Interventions:**
- Methylprednisolone 1 mg/kg per day IV for 7 days (n = 43)
- Saline (n = 43)

**Primary Endpoint:**
- Clinical deterioration at 14 days

**Key Secondary Endpoints:**
- Clinical cure at 14 days
- Median number of days to clinical cure: 14 vs. 12
- ICU admission: 4.8% in both arms
- In-hospital mortality: 0% vs. 2.3%
- Median number of days hospitalized: 17 vs. 13

**Participant Characteristics:**
- Mean age 56 years; 48% men
- Median time from symptom onset to randomization: 8 days
- At randomization, 71% were receiving oxygen via nasal cannula

**Primary Outcome:**
- Clinical deterioration at 14 days: 4.8% in both arms (OR 1.0; 95% CI, 0.134–7.442; \( P = 1.00 \))

**Secondary Outcomes:**
- No differences (all \( P > 0.05 \)) between methylprednisolone arm and placebo arm for:
  - Clinical cure at 14 days: 51% vs. 58%
  - Median number of days to clinical cure: 14 vs. 12
  - ICU admission: 4.8% in both arms
  - In-hospital mortality: 0% vs. 2.3%
  - Median number of days hospitalized: 17 vs. 13

**Key Limitations:**
- Small sample size
- Terminated early because of decreasing incidence of COVID-19 pneumonia at study sites

**Interpretation:**
- The incidence of clinical deterioration did not differ between the methylprednisolone and placebo arms.
### Single-Blind RCT of 3 Doses of Dexamethasone in Hospitalized Patients With Moderate to Severe COVID-19 in Iran

#### Methods
- **Key Inclusion Criteria:**
  - PCR-confirmed SARS-CoV-2 infection or CT scan showing lung involvement
  - Moderate or severe COVID-19
  - Requirement for supplemental oxygen
- **Key Exclusion Criteria:**
  - Uncontrolled DM
  - Active fungal or parasitic infection
  - On MV or receiving vasopressor therapy
- **Interventions:**
  - Low dose: DEX 8 mg IV once daily for up to 10 days (n = 47)
  - Intermediate dose: DEX 8 mg IV twice daily for up to 10 days (n = 40)
  - High dose: DEX 8 mg IV 3 times a day for up to 10 days (n = 46)
- **Primary Endpoint:**
  - Time to clinical response, as measured by OS
- **Key Secondary Endpoints:**
  - Mortality at 60 days
  - Occurrence of AEs

#### Results
- **Participant Characteristics:**
  - Mean age: 59 years in low-dose arm vs. 59 years in intermediate-dose arm vs. 56 years in high-dose arm
  - 50% men
  - 23% with DM
  - 75% received RDV
- **Primary Outcome:**
  - Mean number of days to clinical response: 4.3 in low-dose arm vs. 5.3 in intermediate-dose arm vs. 6.1 in high-dose arm ($P=0.025$)
- **Secondary Outcomes:**
  - Mortality at 60 days: 17% in low-dose arm vs. 30% in intermediate-dose arm vs. 41% in high-dose arm ($P=0.06$)
  - AEs (leukocytosis, hyperglycemia, and secondary infections) occurred more frequently in intermediate-dose and high-dose arms than in low-dose arm; however, this result was not statistically significant.

#### Limitations and Interpretation
- **Key Limitation:**
  - Small sample size
- **Interpretation:**
  - The time to clinical response was significantly shorter in the low-dose DEX arm than in the intermediate- or high-dose arms. Patients in the low-dose arm had a higher probability of survival than those in the high-dose arm.
Open-Label Randomized Trial of High-Dose Versus Low-Dose Dexamethasone in Patients With COVID-19-Related ARDS in Argentina

**Key Inclusion Criteria:**
- Laboratory-confirmed SARS-CoV-2 infection
- ARDS
- On MV for <72 hours

**Key Exclusion Criteria:**
- Presumed imminent death
- Immunosuppression
- Treatment with glucocorticoids

**Interventions:**
- High dose: DEX 16 mg IV once daily for 5 days, followed by DEX 8 mg IV once daily for 5 days (n = 49)
- Low dose: DEX 6 mg once daily IV for 10 days (n = 49)

**Primary Endpoints:**
- Number of ventilator-free days by Day 28
- Time to discontinuation of MV

**Participant Characteristics:**
- Mean age: 60 years in high-dose arm vs. 63 years in low-dose arm
- 30% women

**Primary Outcomes:**
- Median number of ventilator-free days by Day 28: 0 for both arms (P = 0.23)
- No difference between arms in mean duration of MV by Day 28 (19 ± 18 days in high-dose arm vs. 25 ± 22 days in low-dose arm; P = 0.078). Cumulative hazard of successful discontinuation from MV was greater in high-dose arm than low-dose arm (adjusted subdistribution HR 1.84; 95% CI, 1.31–2.5; P < 0.001).

**Secondary Outcome:**
- All-cause mortality:
  - By Day 28: 41% in high-dose arm vs. 39% in low-dose arm (P > 0.999)
  - By Day 90: 47% in both arms (P > 0.999)

**Key Limitations:**
- Small, open-label study
- Trial was prematurely terminated due to low enrollment rate.

**Interpretation:**
- The use of a higher dose of DEX did not increase the median number of ventilator-free days in patients with ARDS due to COVID-19. However, the higher dose shortened the time to discontinuation of MV.
References


