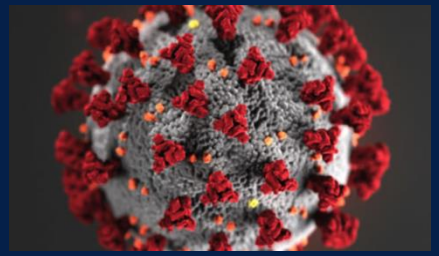

Updates in COVID-19 Therapeutics

August 5, 2020

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Division of Infectious Diseases
University of California, San Francisco

Scientific Panel:

WHO Collaborating Center for HIV Surveillance
Modeling in Health Research Center
Institute for Futures Studies in Health
Kerman University of Medical Sciences

UCSF

Outline

- Clinical Course and Treatment Overview
- Antivirals
- Immune modulators

Outline

- **Clinical Course and Treatment Overview**
- Antivirals
- Immune modulators

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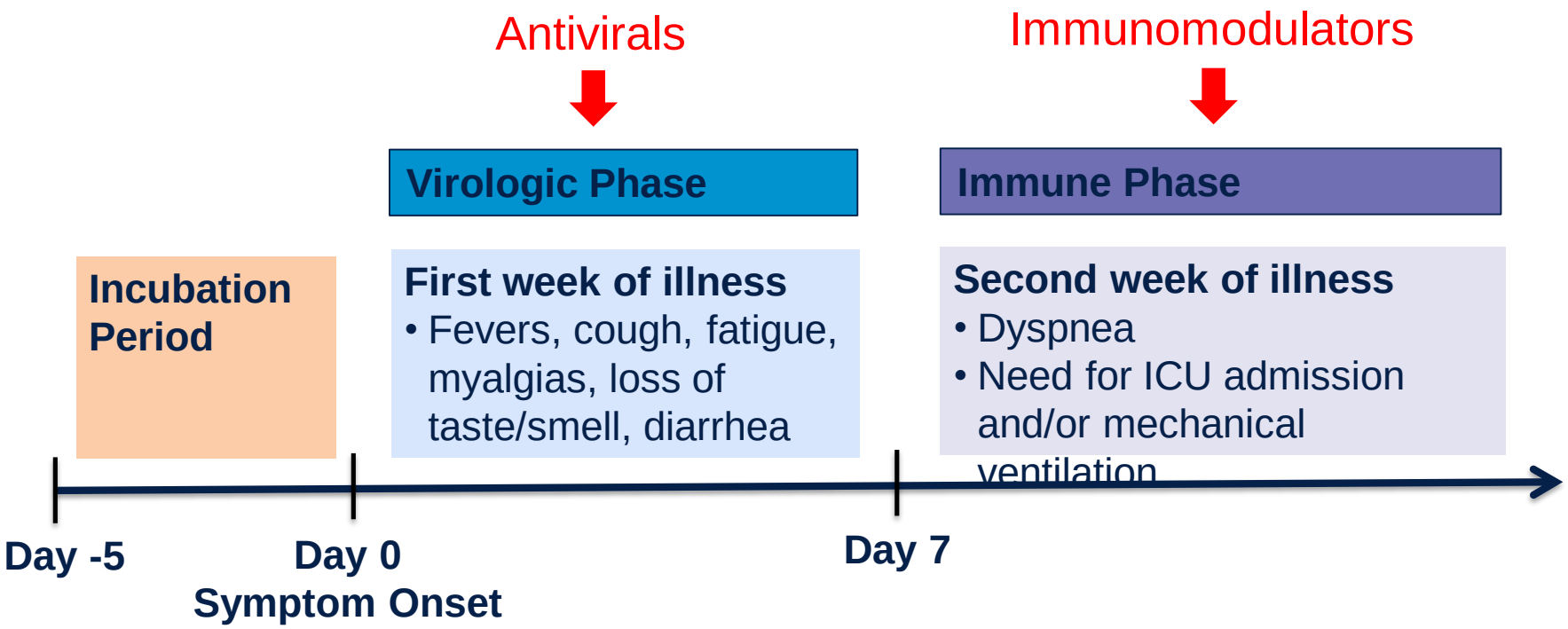
Clinical Course and Treatment



Treatment Overview

Antivirals
- Remdesivir
- Convalescent plasma
- Hydroxychloroquine
- Protease Inhibitors

Immunomodulators
- Steroids
- Convalescent plasma
- JAK/cytokine inhibitors
- Interferon

Treatment Overview

Antivirals

- Remdesivir ✓
- Convalescent plasma?
- ~~Hydroxychloroquine~~
- ~~Protease Inhibitors~~

Immunomodulators

- Steroids ✓
- Convalescent plasma?
- JAK/cytokine inhibitors?
- Interferon?

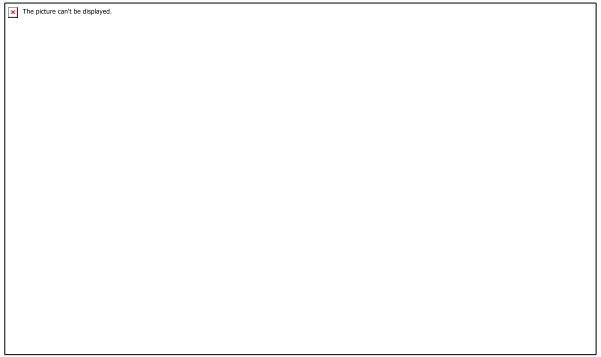
Outline

- Clinical Course and Treatment Overview
- **Antivirals**
- Immune modulators

Remdesivir: Early studies

Mechanism: Nucleoside analog that inhibits RNA-dependent RNA polymerase

- Active in vitro
- Clinical benefit in macaques
- Compassionate use study showed promise (but no control group)



Wang et al, Cell Research 2020. Williamson, Nature 2020. Grein et al, NEJM. 2020..

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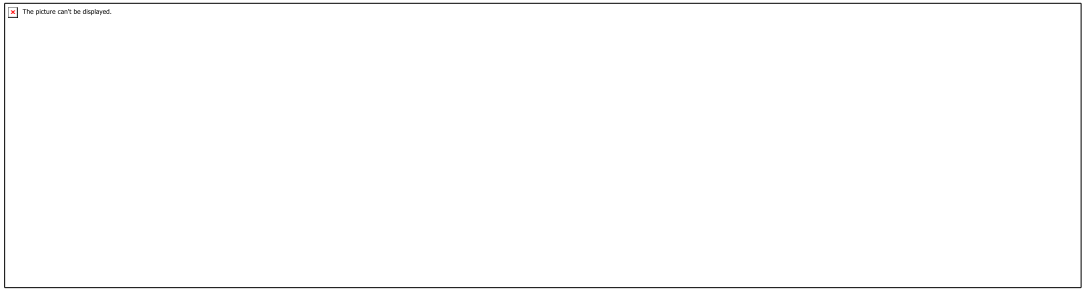
Remdesivir: RCT from China



RCT of 237 adults with COVID and:

- ≤12d symptoms
- SaO2 ≤94% on RA
- PNA on imaging

Randomized to RDV vs placebo x 10 days

- No difference in time to clinical improvement
- No difference in viral load clearance

Did not meet pre-specified enrollment target (n=325) so was underpowered to detect a clinical benefit

Wang et al, Lancet 2020.

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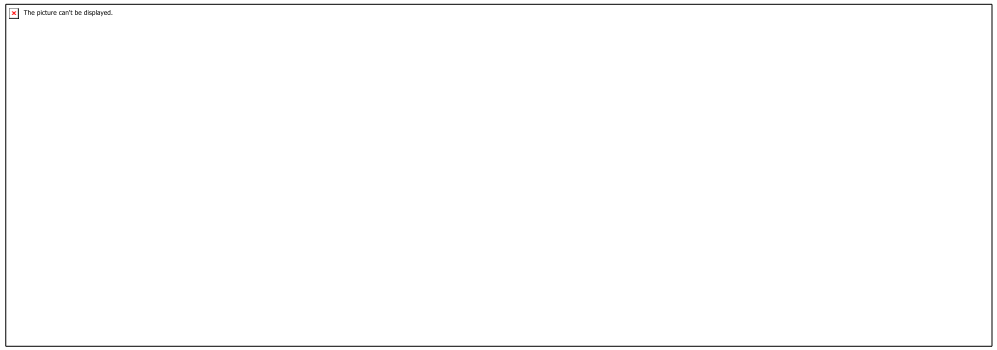
Remdesivir: ACTT-1 Study



RCT of 1063 adults with COVID-19 and one of:

- Radiographic infiltrates
- SaO2 ≤ 94% on RA
- Needing supplemental O2

Randomized to RDV vs placebo x 10 days

- Shortened recovery time from 15 to 11d ($p<0.001$)
- 14d mortality: remdesivir (7%) vs placebo (12%), but not significant

Beigel et al, NEJM 2020.

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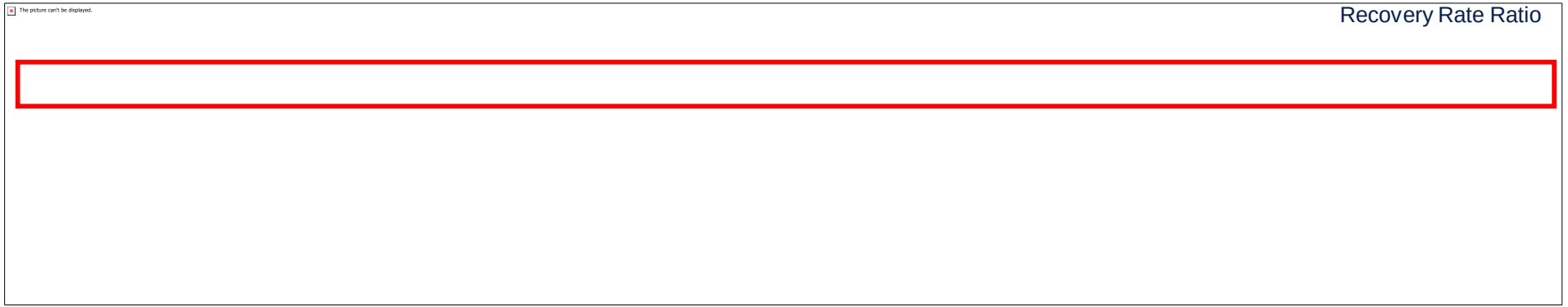
RDV: Most Benefit if on Supplemental O2 only?



- However, concern that intubated patients may require a longer follow-up time in order to see clinical benefit, and trial was not powered to look at these subgroups
- More to come when final results of the trial are published

Beigel et al, NEJM 2020.

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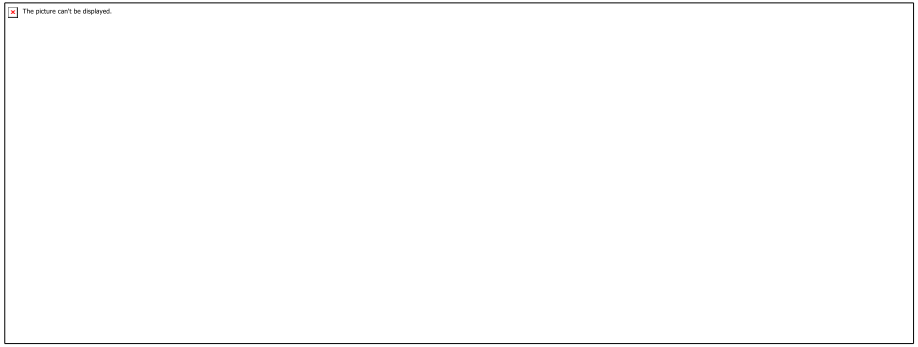
Remdesivir: Duration (SIMPLE Study)



- RCT of 397 patients with COVID (similar inclusion criteria to ACTT-1)
- No difference in efficacy in 5 vs. 10 days of RDV
- Very few patients were on mechanical ventilation

Bottom Line: Most patients can get 5 days, although can consider 10 days if mechanically ventilated and not improving

Goldman et al, NEJM 2020.

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Remdesivir: Ongoing Studies

- ACTT-2: remdesivir plus baricitinib vs placebo (finished enrollment)

- ACTT-3: remdesivir plus IFN-ß1a subq vs placebo (has not started enrollment yet)

Remdesivir: Conclusions

- Now standard of care in the US:
  - Give via Emergency Use Authorization (hospitalized, $SaO_2 \leq 94\%$ RA or on supplemental O_2 of any level)
  - Controversial whether or not to prioritize those only on supplemental O2 (not HFNC or MV) if there are drug shortages
- Contraindicated if ALT ≥ 5x ULN, consider risk/benefit if CrCl<30 (cyclodextran)
- Do not give with HCQ → can reduce antiviral activity of remdesivir
- Duration 5 days (can consider 10d if intubated and not improving)

Hydroxychloroquine (HCQ)

Mechanism: inhibits endosome-mediated viral entry and glycosylation of envelope proteins

- Active in vitro and early clinical reports showed promise (but no control groups)
- Now multiple RCTs show no benefit and most also show an increased risk of adverse effects (reviewed on next slide)
- FDA has revoked its Emergency Use Authorization for HCQ
- Both NIH and IDSA guidelines recommend against using HCQ unless part of a clinical trial

Wang et al, Cell Research 2020.

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Hydroxychloroquine RCTs

Hospitalized Patients

- **Coalition trial**: no clinical improvement with HCQ +/- azithro, ⇧QT
- **Tang et al, BMJ**: no benefit in viral clearance, ⇧ AEs
- **Recovery trial (preprint)**: no difference mortality, ⇧ risk composite intubation/death
- Other trials have been stopped early for lack of benefit (press releases)

Outpatients

- **Mitja et al, CID**: no benefit in viral load reduction or time to symptom resolution, no diff in AEs
- **Skipper et al, Annals**: no reduction in symptom severity, increased risk AEs

Prophylaxis Trials

- **Boulware et al, NEJM**: no benefit in preventing infection after exposure, ⇧ AEs

Horby et al, medRxiv. Tang et al, BMJ 2020. Calvacanti et al, NEJM. Mitja et al, CID 2020. Skipper et al, Annals Int Med 2020. Boulware et al, NEJM 2020.

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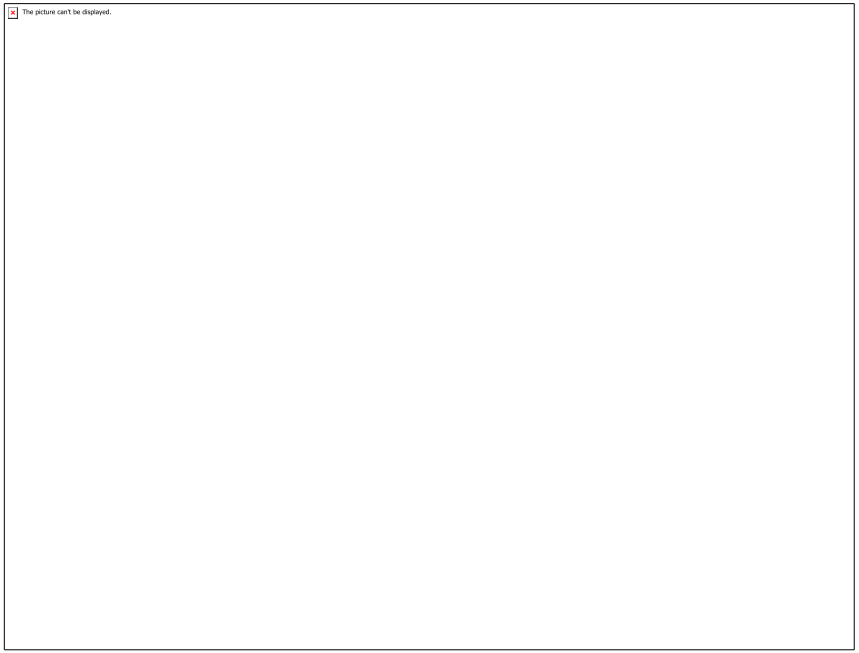
Lopinavir/ritonavir

Mechanism: postulated to act against proteases of SARS-CoV-2 (controversial)

- RCT of 199 patients
- No difference in time to improvement, mortality, changes in viral load
- Caveat: patients started the drug late (median 13d of symptoms)



Cao et al, NEJM 2020.

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Darunavir/cobicistat

- RCT of 30 patients with mild COVID (SaO2 >93% RA) who received inhaled IFN with or without 5 days of DRV/c
- No difference in viral clearance or time to defervesence

- Both NIH and IDSA guidelines recommend against using LPV/r or other PIs unless part of a clinical trial

Chen et al, OFID 2020.

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Antivirals: Conclusions

- Remdesivir → YES

- Hydroxychloroquine → NO
- Lopinavir/ritonavir or other protease inhibitors → NO

Outline

- Clinical Course and Treatment Overview
- Antivirals
- **Immune modulators**

Steroids

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Dexamethasone in Hospitalized Patients with Covid-19 — Preliminary Report

The RECOVERY Collaborative Group*

RCT of 6425 patients with COVID-19 and:

- No contraindication to dex per the treating attending
- ~2000 patient excluded, reasons not reported

Randomized to dex 6mg IV/PO vs placebo x 10 d (or until d/c)

Very few patients got remdesivir or plasma

28 day mortality:

22.9% dex group vs 25.7% placebo group ($p<0.001$)

Recovery trial, NEJM 2020.

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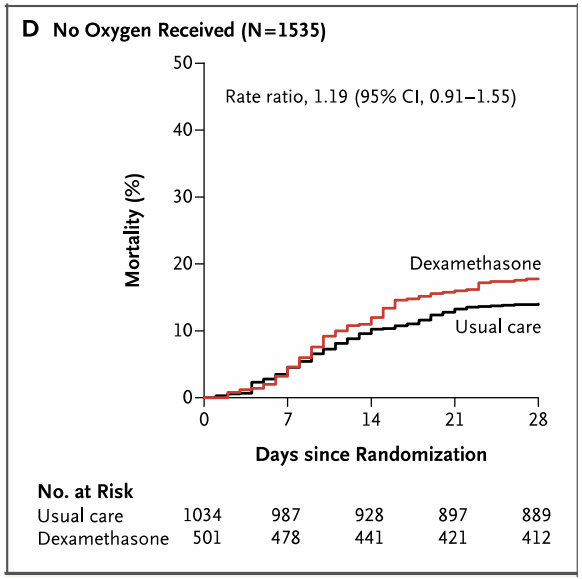
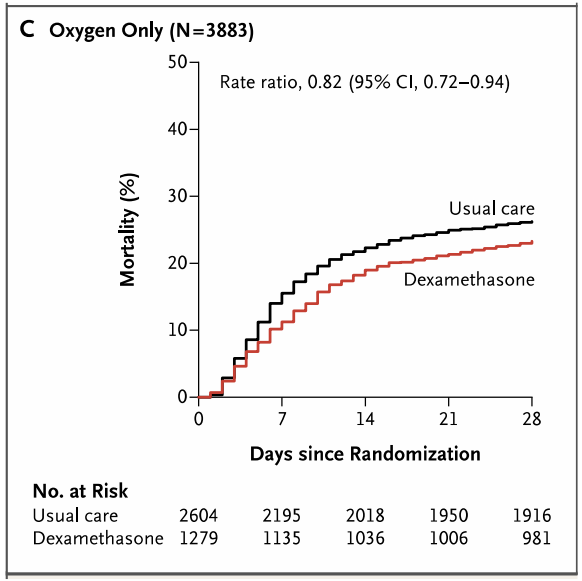
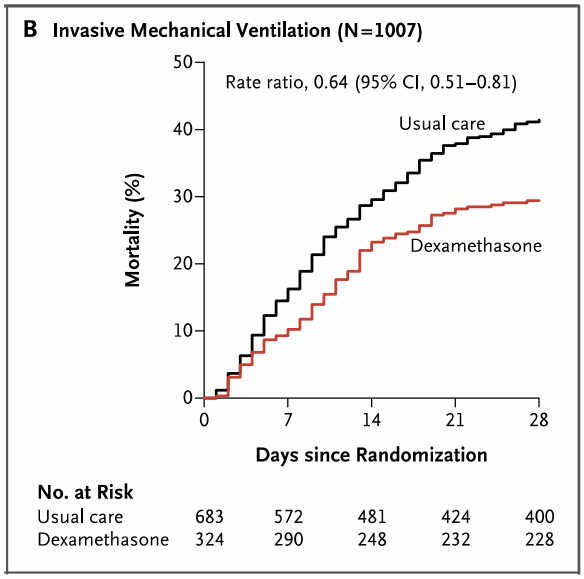
Dexamethasone by Level of Oxygen







No oxygen
Dex 17.8%
Usual care 14.0%

Supplemental O2
Dex 23.3%
Usual care 26.2%

Mechanical ventilation
Dex 29.3%
Usual care 41.4%

Recovery trial, NEJM 2020.

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Dexamethasone: Issues with the Study

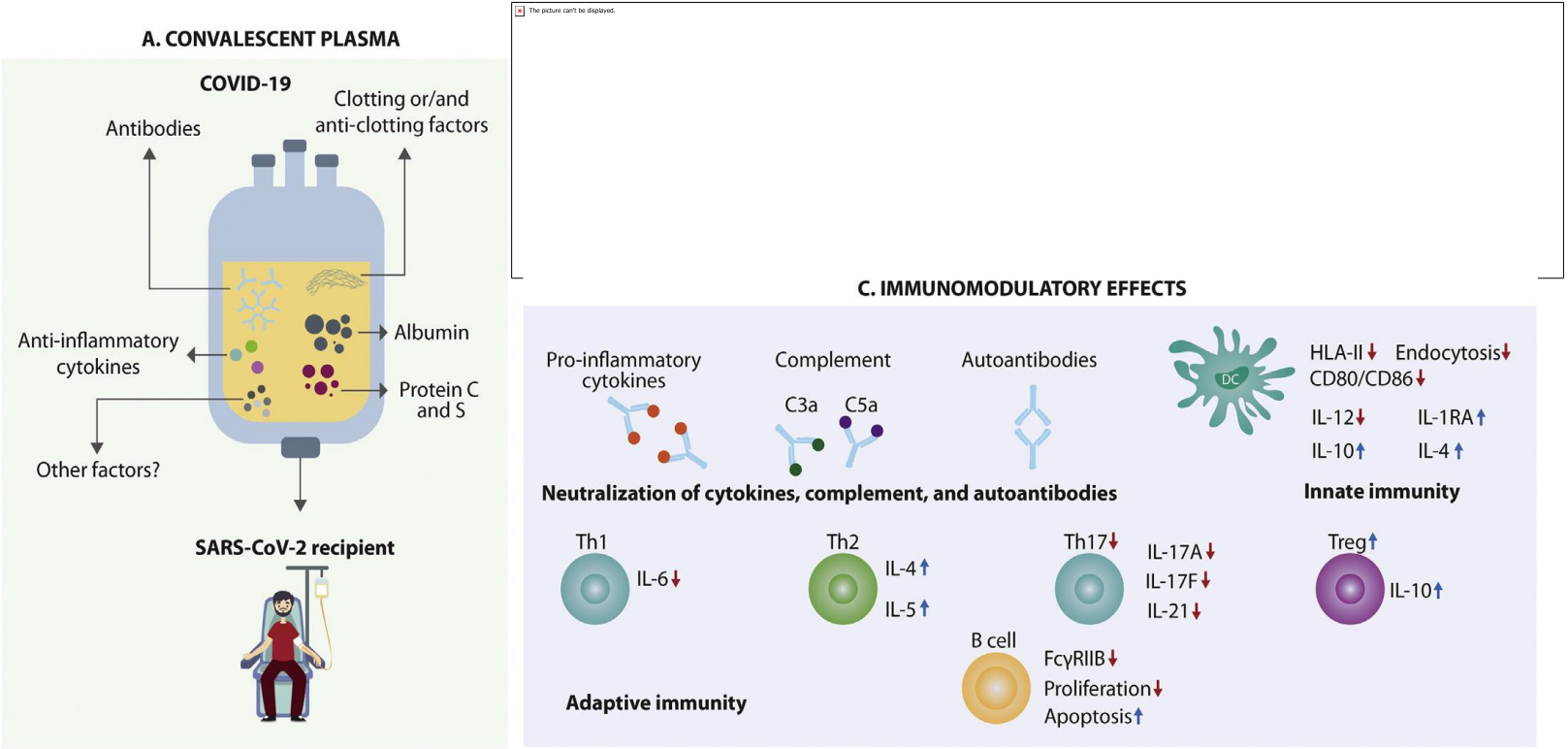
- Patient selection:
  - 25% had diabetes but very few immunocompromised
  - Unclear who was excluded
- Did not report by level of O2 → is benefit same at 2L vs 15L HFNC?
- High mortality rate in the study
  - Unclear what benefit would be in a lower mortality rate setting
  - What would be impact of remdesivir (now standard of care)?
- Side effects of steroids not reported (hyperglycemia, infections, etc)

Recovery trial, NEJM 2020.

Dexamethasone: Conclusions

- Room air → do not give dexamethadone
- Mechanical ventilation → give dexamethasone
- Supplemental O2 →
  - NIH/IDSA guidelines recommend to give dexamethasone
  - UCSF: we reserve dex for those on ≥3-4 L and weigh risks/benefits

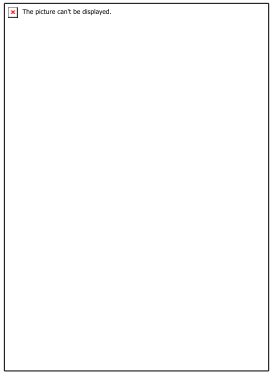
Convalescent Plasma: Mechanism of Action



Rojas et al, Autoimm Rev 2020.

Convalescent Plasma: Observational Data

- Several small case series of critically ill patients who improved after getting CP (but no control groups)
- Case control study of 39 patients treated with plasma (preprint): decreased mortality in plasma group, especially for non-intubated patients
- Expanded access program report of 5000 patients → adverse effects in <1%, no signal of toxicity beyond that expected from plasma use in severely ill patients



Shen et al, JAMA 2020. Duan et al, PNAS 2020. Joyner et al, JCI 2020.. Liu et al, medRxiv.

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Convalescent Plasma: RCT

JAMA | Original Investigation

Effect of Convalescent Plasma Therapy on Time to Clinical Improvement in Patients With Severe and Life-threatening COVID-19
A Randomized Clinical Trial

RCT of 103 patients with severe or life-threatening COVID-19

- Symptom duration = 30d
- Study terminated early, may have been underpowered

Randomized to convalescent plasma vs standard treatment

(not blinded)

- No difference in time to improvement or mortality
- Possible signal for ⇧ improvement in severe group
- Higher rate of viral clearance in plasma group

Li et al, JAMA 2020.

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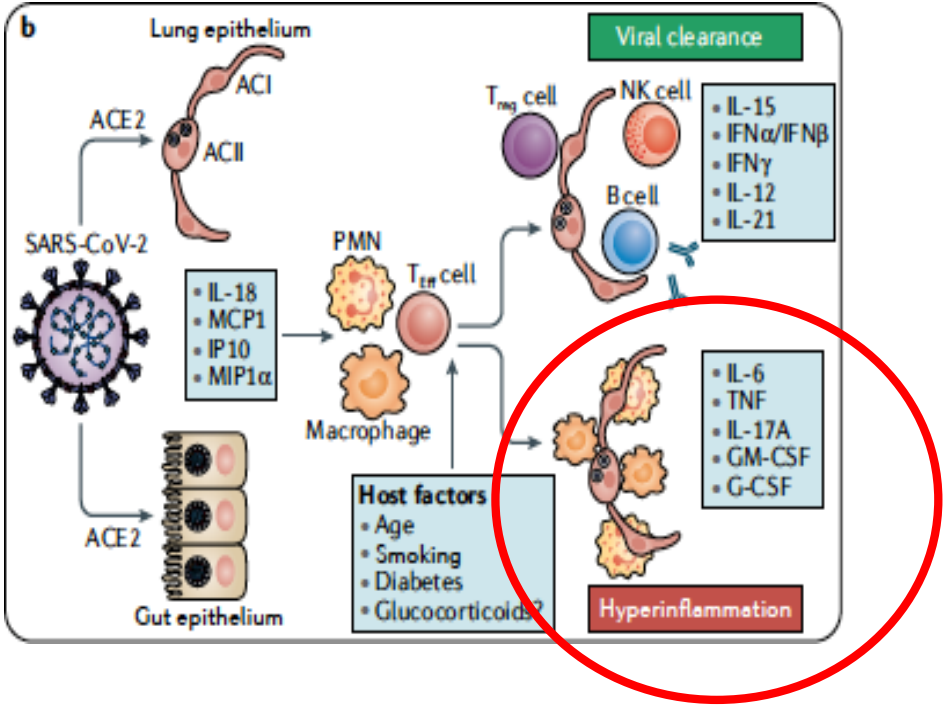
Convalescent Plasma: Conclusions

- Unclear benefit but appears safe
- More RCTs are underway
- Guidelines:
  - IDSA guidelines: recommend to give convalescent plasma only within a clinical trial
  - NIH: insufficient evidence to recommend for or against
  - In practice: routinely given but practice patterns vary

Biologics (Cytokine and JAK inhibitors)

- Rationale is to suppress the inflammatory response that may have a role in disease pathogenesis
- Case series report possible benefit (but no control groups)
- Many RCTs underway



Moore and June, Science 2020.

Tocilizumab (Anti-IL6R)

- Several case reports/case series reporting benefit (no control group)
- Recent retrospective study of 154 intubated patients (78 received toci, 76 did not): 45% reduction in death but 2-fold increase in superinfections (in particular *S. aureus* pneumonia)
- Meta-analysis of 7 retrospective studies (n=593): no effect on mortality, ICU admission, need for intubation
- COVACTA study, RCT (press release): no effect on clinical status or mortality

Somers et al, CID 2020. Lan et al, IJAA 2020.

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Tocilizumab: Conclusions

- Guidelines:
  - IDSA: recommend to give tocilizumab only within a clinical trial
  - NIH: insufficient evidence to recommend for or against
  - In practice: commonly used at some centers (we do not use at UCSF)

Interferon

- **Triple therapy RCT**: 86 patients with LPV/r + ribavirin + interferon ß-1b vs 41 patients who got LPV/r alone → Triple therapy group had more rapid viral clearance, shorter symptom duration and LOS

- **Small RCT** of 42 patients (IFN ß-1a) vs 39 patients getting standard of care (HCQ + PI, study in Tehran in March) → time to clinical response unchanged but lower mortality in IFN group

- NIH guidelines: recommend against except in setting of a clinical trial (not addressed in IDSA guidelines)

- Will be studied in ACTT-3 trial (remdesivir + IFN ß-1a vs placebo)

Hung et al, Lancet 2020. Davoudi-Monfared et al, AAC 2020.

Immunomodulators: Conclusions

- Dexamethasone → YES

- Convalescent plasma → ?
- Immunomodulators → ?
  - Tocilizumab → probably NO
  - Interferon → ?

Treatment Overview

Antivirals

- Remdesivir ✓
- Convalescent plasma?
- ~~Hydroxychloroquine~~
- ~~Protease Inhibitors~~

Immunomodulators

- Steroids ✓
- Convalescent plasma?
- JAK/cytokine inhibitors?
- Interferon?

Resources

- IDSA Treatment Guidelines: https://www.idsociety.org/practice-guideline/covid-19-guideline-treatment-and-management/

- NIH Treatment Guidelines: https://files.covid19treatmentguidelines.nih.gov/guidelines/covid19treatmentguidelines.pdf

Questions?