Pediatric Considerations

A Review of Pertinent Drug Information for SARS-CoV-2

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Data as of 8/10/20

COVID-19 Adults vs Children

Children are not little adults

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Remdesivir (GS-5734)

- **Mechanism of Action**: interference with viral RNA polymerase leading to premature termination of viral RNA transcription

- **Investigational agent**
  - Authorized and available for emergency use in severe SARS-CoV-2 Infection
  - Available through Gilead for compassionate use in pediatrics (https://rdvcu.gilead.com/)

- **Pharmacokinetic Highlights**
  - Phosphoramidate prodrug, CYP3A4 substrate
  - Active metabolite half-life of 20.4-25.3 hours
  - Eliminated 63% renally

Inclusion	Exclusion
1. SARS-CoV-2 Positive 2. ALT levels < 5x ULT 3. Hospitalized with SaO2 < 94 % on room air or supplemental O2	1. Significant vasopressor or inotropic support 2. Requiring VA ECMO 3. Creatinine Clearance < 30 mL/min, HD, or CVVH

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Personal Communication, Gilead, accessed 8/3/20

Remdesivir Dosing

Adult and Children ≥ 40 kg

- 200 mg/dose IV on day 1 followed by 100 mg/dose IV q24h on days 2-5
- Treatment may be extended up to 10 days for lack of clinical improve

Gilead: "Exposure comparable to that observed in adults while limiting the exposure of the nucleoside analog GS-441524"

Children 3.5 kg to < 40 kg

- 5 mg/kg/dose IV on day 1 followed by 2.5 mg/kg/dose IV on days 2-5,
  - Treatment may be extended up to 10 days for lack of clinical improvement
- Dosing recommended for:
  - Post-natal age > 7 days
  - Full-term
  - Serum creatinine < 1 mg/dl

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Personal Communication, Gilead, accessed 8/3/20
Ebola R&D Blueprint, WHO, accessed 4/18/20

Remdesivir Formulations

Solution

- Use in adults and pediatric patients ≥ 40 kg
- Contains 6 g of cyclodextrin per 100 mg of remdesivir
  - Intravenous voriconazole has 3.2g per 200 mg dose

Lyophilized Powder

- Use in pediatric patients 3.5 to < 40 kg
  - Intravenous solution should not be used in this age group
- Contains 3 g of cyclodextrin per 100 mg of remdesivir

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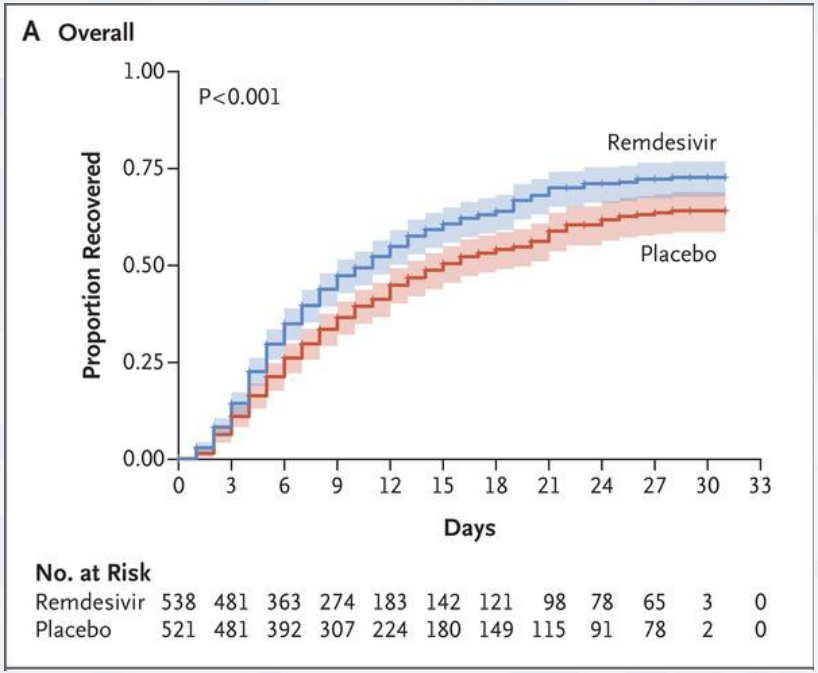
Personal Communication, Gilead, accessed 8/3/20

COVID-19 Efficacy Data

Randomized, placebo-controlled trial (ACTT-1)

- 1063 adult patients, 538 and 521 randomized to remdesivir and placebo, respectively
- Median time-to-recovery of 11 days vs 15 days (rate ratio for recovery, 1.32; 95% CI, 1.12 to 1.55; P<0.001)
- No statistical difference in 14-day mortality (hazard ratio for death, 0.70; 95% CI, 0.47 to 1.04)



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No published pediatric data, studies ongoing

Beigel J, et al. N Engl J Med 2020.

Safety Data

Adult compassionate use

- 60% reported adverse events
- Most common: **increased hepatic enzymes**, diarrhea, rash, renal impairment, hypotension
- No comparator arm, confounded by COVID-19

ACTT-1 Trial

- Well tolerated overall
- Higher rate of adverse events in the placebo group than remdesivir
  - AST/ALT elevation was 7.4 and 7.3% in the remdesivir and placebo groups, respectively

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Grein J, et al. N Engl J Med. 2020 Apr 10.
Beigel J, et al. N Engl J Med 2020.

Hydroxychloroquine

- Antimalarial and immunomodulatory agent
- **Mechanism of Action:**
  - Impaired viral receptor glycosylation and intracellular alkalization inhibiting viral replication
  - Reduces cytokine production and inhibits toll-like receptor signaling
- **Supplied as Tablets**
  - May be compounded into suspension for patients unable to take tablets

Adverse-Events

Rash
Retinopathy (chronic use)
Hypoglycemia
Gastrointestinal disturbances
QTc prolongation

Caution use with other QTc prolonging agents

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Ben-Zvi I et al. Clin Rev Allergy Immunol 2012;42(2):145-53.
McHenry A, et al. *Int J Pharm Compd*. 2017;21(3):251-254.

Hydroxychloroquine Dosing

Indication	Pediatric Oral Dose	Max Oral Dose
Rheumatologic Condition	3 – 5 mg/kg/day divided in 1-2 doses	400 mg/day or 7 mg/kg/day
Malaria	13 mg/kg/dose followed by 6.5 mg/kg/dose at 6, 24, 48 hours after first dose	800 mg/dose followed by 400 mg/dose at 6, 24, 48 hours after initial dose
COVID-19 (Yao X, et al)	6.5 mg/kg/dose BID on day 1 then 3.25 mg/kg/dose BID on days 2-5	400 mg/dose BID on day 1 then 200 mg/dose BID on days 2-5
COVID-19 (Downes K, et al)	13 mg/kg/dose followed by 6.5 mg/kg/dose at 6, 24, 48 hours after initial dose	800 mg/dose followed by 400 mg/dose at 6, 24, 48 hours after initial dose

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Yao X, et al. Clin Infect Dis 2020 Mar 9
Downes K, et al. OSF pre-print 2020 Mar 31

Combination with Azithromycin?

- Azithromycin not routinely indicated in pediatric bacterial community acquired pneumonia unless atypical bacteria suspected
- No pediatric data on combination to support use
- Potential harm from routine combination and use of azithromycin when not otherwise indicated
  - ↑ Risk of QTc prolongation
  - ↑ Antibiotic resistance

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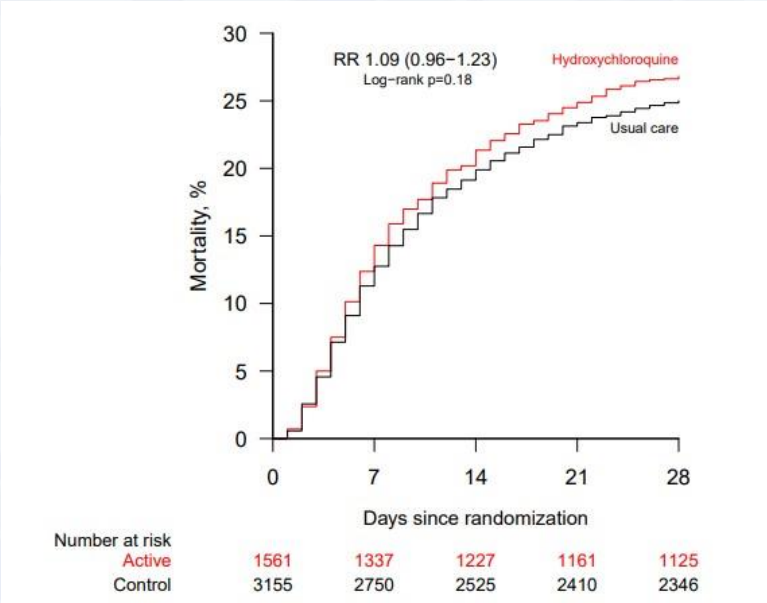
Bradley J. Clin Infect Dis. 2011 Oct;53(7):e25-76.

RECOVERY Trial

Adult Randomized Controlled Open-label Trial

Author's Conclusion: "Hydroxychloroquine was not associated with reductions in 28-day mortality but was associated with an increased length of hospital stay and increased risk of progressing to invasive mechanical ventilation or death"



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Horby P, et al. https://www.medrxiv.org/content/10.1101/2020.07.15.20151852v1.full.pdf.

Dexamethasone

- Corticosteroid

- **Mechanism of Action:**
  - Anti-inflammatory and immunomodulatory via multiple mechanisms

- **Dosing (IV/PO)**
  - **Recovery trial:** 6 mg/dose q24h for 10 days
  - **Pediatric dose:** 0.15 mg/kg (max 6 mg) q24h

Drug Interactions
- Interactions with CYP3A4 inhibitors and inducers

Adverse Events

Hyperglycemia
Leukocytosis
Hypernatremia
Hypokalemia
Fluid retention and edema
Insomnia and other neuropsychiatric events
Gastrointestinal bleeds

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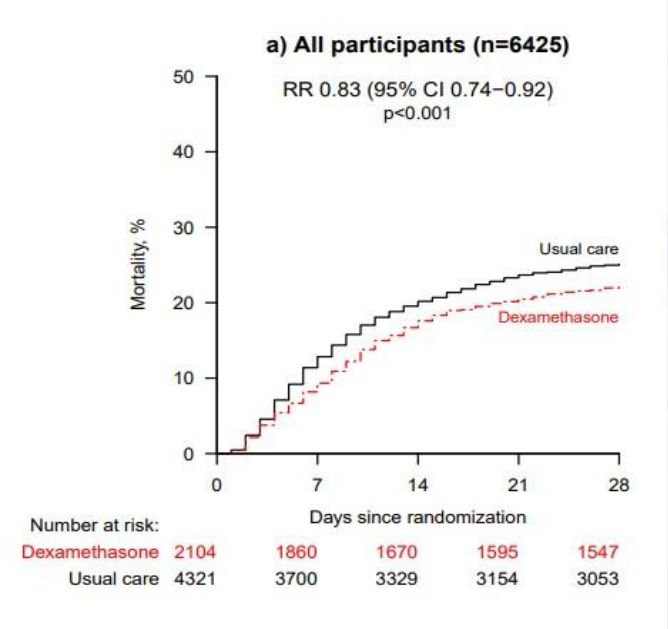
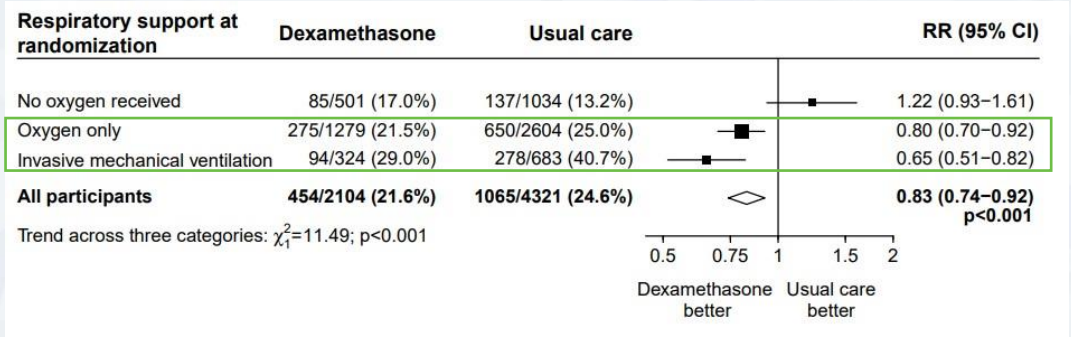
Dexamethasone Injection [prescribing information]. Lake Zurich, IL: Fresenius Kabi; November 2017.
Horby P, et al. https://www.medrxiv.org/content/10.1101/2020.06.22.20137273v1.full.pdf.

RECOVERY Trial





Author's Conclusion: "Dexamethasone reduced 28-day mortality among those receiving invasive mechanical ventilation or oxygen at randomization, but not among patients not receiving respiratory support"

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Horby P, et al. https://www.medrxiv.org/content/10.1101/2020.06.22.20137273v1.full.pdf.

Lopinavir/Ritonavir

- **Mechanism of Action:**
  - Lopinavir - HIV protease inhibitor
  - Ritonavir - HIV protease inhibitor, but in combination with lopinavir (LPV/r) is acting as a CYP3A4 inhibitor that increases lopinavir concentrations
  - Inhibits the protease of SARS-CoV-2 inhibiting viral replication

- **Monitor for Drug-drug interactions**
  - Major substrate and inhibitor of cytochrome P450 enzymes
  - Must screen for drug-drug interactions

Adverse-Events

GI distress Hepatotoxicity
Pancreatitis
Diabetes
QTc prolongation
Lipid elevations and fat redistribution

University of Liverpool Drug-Interaction Resource
https://www.covid19-druginteractions.org/

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Kaletra (lopinavir and ritonavir) tablets and oral solution [prescribing information]. North Chicago, IL: AbbVie Inc; March 2020.

Lopinavir/Ritonavir Dosing

- **Adults**
  - Lopinavir 400 mg/ritonavir 100 mg PO twice daily
- **Children**
  - Dosed based on lopinavir component with two recommended doses
    1. Lopinavir 300 mg/m^2/dose PO (maximum 400 mg/dose) twice daily
    2. Lopinavir 16 mg/kg/dose PO (maximum 400 mg/dose) twice daily

Approximate Lopinavir 300 mg/m^2 Dose Recommendations	
Weight	**Dose**
15 – 20 kg	200 mg BID of lopinavir
21 – 30 kg	300 mg BID of lopinavir
> 30 kg	400 mg BID of lopinavir

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Kaletra (lopinavir and ritonavir) tablets and oral solution [prescribing information]. North Chicago, IL: AbbVie Inc; March 2020.

RECOVERY Trial

1596 patients were randomized to lopinavir-ritonavir and 3376 patients randomized to usual care

Oxygen Status at Baseline

- 4% required invasive mechanical ventilation
- 70% required oxygen alone
- 26% did not require any respiratory intervention

Primary outcome was 28-day mortality

- 22.1% lopinavir-ritonavir vs. 21.3% usual care (RR 1.04 [95% CI 0.91- 1.18]; p=0.58)
- No beneficial effects in 28-d mortality, progression to mechanical ventilation or length of stay

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Horby P, et al.https://www.recoverytrial.net/news/. Accessed 8/10/20

Multisystem Inflammatory Syndrome in Children (MIS-C)

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MIS-C

- Similar in presentation to Kawasaki's Disease (KD) and Toxic Shock Syndrome
- Likely to receive treatment for KD if criteria met
  - Intravenous immunoglobulin and aspirin
- Refractory MIS-C treatment is an active area of investigation
  - Anakinra and tocilizumab have been proposed

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CDC. https://www.cdc.gov/mis-c/. Accessed 8/10/20

Tocilizumab

- **Mechanism of Action**: monoclonal antibody against human interleukin type 6 (IL-6) receptor

- Published use of agent limited to adults with COVID-19
  - FDA-approved for cytokine release syndrome and several rheumatologic conditions in those ≥ 2 years old

Dosing:

- 4-8 mg/kg/dose once followed by a one-time repeat dose after 12 hours if lack of clinical improvement (max 800 mg/dose)
- Should we use higher doses in pediatrics?

Children < 30 kg: 12 mg/kg/dose?

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Xu X, et al. 2020. https://t.co/2LmKN34HjM?amp=1

COVID-19 Efficacy

n=21 adult patients,
mean age 57 years old

Author Conclusions:

"Tocilizumab effectively improved clinical symptoms and repressed the deterioration of severe COVID-19 patients"

Table 2. Laboratory Tests Before and After Tocilizumab

	Range	Before the tocilizumab	After the tocilizumab		
			D1	D3	D5
White-cell count, $\times 10^9$/L	3.5-9.5	6.30 ± 2.77 (4/20, 20.0%)	8.05 ± 4.39 (8/18, 44.4%)	6.02 ± 3.05 (9/21, 42.9%)	5.25 ± 2.11 (2/19, 10.5%)
Lymphocyte percentage, %	20-50	15.52 ± 8.89 (17/20, 85.0%)	11.78 ± 11.36 (16/18, 88.9%)	16.93 ± 13.59 (14/21, 66.7%)	22.62 ± 13.48 (9/19, 47.4%)
C-reactive protein, mg/L	0-5	75.06 ± 66.80 (20/20, 100%)	38.13 ± 54.21 (17/18, 94.4%)	10.61 ± 13.79 (10/20, 50.0%)	2.72 ± 3.60 (3/19, 15.8%)
Procalcitonin, ng/ml	0-0.5	0.33 ± 0.78 (2/20, 10.0%)	0.21 ± 0.35 (2/16, 12.5%)	0.09 ± 0.13 (1/19, 5.3%)	0.12 ± 0.15 (1/18,5.6%)

Data are means ± SD (abnomal no./total no., %).

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Xu X, et al. 2020. https://t.co/2LmKN34HjM?amp=1

COVACTA Top-Line Results

- Phase III, randomized, double-blind, placebo-controlled study evaluating tocilizumab in severe COVID-19 pneumonia in adult hospitalized patients

- **Clinical Results**
  - The primary endpoint was change in clinical status, no difference was found (p=0.36; OR [95% CI] = 1.19 [0.81, 1.76])
  - No difference in 28-day mortality (tocilizumab = 19.7% vs placebo = 19.4% [95% CI] of 0.3% [-7.6%, 8.2%], p=0.9410)
  - Ventilator-free days (22 days for tocilizumab vs 16.5 days for placebo, [95% CI] = 5.5 [-2.8, 13.0], p=0.3202)
  - Time to discharge was shorter in patients treated with tocilizumab than placebo (20 days vs 28 days, p=0.0370)
    - The difference cannot be considered statistically significant as the primary endpoint was not met

- **Infection rates were also similar between tocilizumab vs placebo**
  - Overall infection rate: 38.3% and 40.6%
  - Severe infection rate: 21.0% and 25.9%

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What does this mean for pediatrics and MIS-C treatment?

Roche. https://www.roche.com/investors/updates/inv-update-2020-07-29.htm. Accessed 8/3/20

Anakinra

- Recombinant human interleukin-1 receptor antagonist
- **Mechanism of Action:** Competitively inhibits IL-1 binding to interleukin-1 receptor
- **Adverse Reactions:**
  - Increased incidence of serious infection (Black box warning)
  - Hypersensitivity reaction (Black box warning)
  - Injection site reactions, headache, vomiting, GI disturbance, arthralgias
- **Drug Interactions:**
  - Avoid live vaccines

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Anakinra [Package Insert]. Swedish Orphan Biovitrum AB (2018)

Anakinra Dosing

- Dosing varies on the indication (JIA,NOMID, KD, rheumatoid arthritis, etc…)
- **Routine dosing:**
  - 1-2 mg/kg/day in 1-2 divided doses
  - Maximum of 8 mg/kg/day

Renal adjustment for CrCl < 30 mL/min to every other day administration suggested

- Optimal dose not established for severe COVID-19 or MIS-C
  - Intravenous vs subcutaneous?
  - High-dose (> 400mg/day) vs low-dose (100-200 mg/day)?
  - Should we taper? What is the ideal taper?

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Anakinra [Package Insert]. Swedish Orphan Biovitrum AB (2018)
Cavalli G, et al. Lancet Rheumatol. 2020 Jun;2(6):e325-e331.
Mehta P, et al. Review Lancet Rheumatol. 2020 May 4;2(6):e358-e367.

Summary

- Must scrutinize the evidence closely
- There is currently no proven evidenced-based treatment for COVID-19 in pediatrics
- Must consider the benefit-risk ratio of any medication used for COVID-19 in pediatrics

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Photo by Omar Lopez on Unsplash

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Data as of 8/10/20