Indiana University Health

Updated 5/5/2020
Endorsed by IUHP Infectious Diseases Physicians and ID Pharmacy

Indiana University Health Adult Non-AAHC Inpatient Management of Confirmed SARS-CoV-2 (COVID-19)

No regimen is FDA approved for the treatment of COVID-19. Therapy decisions are based on limited in-vitro, animal, and human data.
Recommendations subject to change as data becomes available.

Mild Disease
SpO_2 > 94% on room air WITH OR WITHOUT radiographic evidence of pneumonia

→ **Supportive Care**

Moderate Disease
SpO_2 ≤ 94% on room air WITH OR WITHOUT radiographic evidence of pneumonia

→ **Assess for Eligibility for Convalescent Plasma≠**

→ **Supportive Care¥**

Severe Disease
SpO_2 ≤ 94%, RR ≥ 30 breaths/min, PaO_2/FiO_2 ≤ 300 mmHg OR Mechanical Ventilation

→ **Assess for Eligibility for Convalescent Plasma≠**

If patient does not meet criteria:
Supportive Care¥

May be added on a case-by-case basis if criteria are met¥:
Tocilizumab 4-8 mg/kg based on total body weight (max 800 mg per dose) x 1, may repeat in 12hr if no clinical improvement and all criteria continue to be met (2 doses max)
Use dependent on joint ICU/ID decision making conversation

Recommended labs for mild/moderate disease:
Baseline, then every 72 hours: CBC w/diff, CMP, CRP, LDH, Ferritin, D-dimer
May repeat earlier with clinical deterioration

Recommended labs for severe disease:
Daily: CBC w/diff, CMP, LDH, Ferritin, D-dimer, Fibrinogen, CRP
If considering tocilizumab: IL-6 x 1 prior to initiation

IU Health COVID-19 Therapies (Locations outside of the AAHC)

¥**Hydroxychloroquine**: We have considered recent pre-print studies and judged the risk of hydroxychloroquine outweighs the possible benefits and **no longer recommend** its use. See attached chart for a summary of the literature. If through the shared decision-making process, a patient or their healthcare proxy wish to pursue treatment with hydroxychloroquine, the most commonly studied dose is 400 mg PO BID x 2 doses, followed by 400 mg PO once daily x 4 doses.
Safety recommendations: Obtain baseline EKG, review medication list for QT-prolonging medications, and consider β-HCG if of childbearing potential. Do not use HCQ if baseline QTc > 500 msec.
Lab monitoring: Recommend daily K and Mg. Keep K ≥ 4 mEq/L and Mg ≥ 1.5 mEq/L.
If discharged prior to completing an inpatient hydroxychloroquine regimen, repeat EKG prior to discharge.
If QTc > 500 msec, do NOT continue hydroxychloroquine on discharge.
If home meds were held due to QTc prolongation, please continue to hold until hydroxychloroquine is completed.

≠Convalescent plasma inclusion criteria (must meet all 5)

1. Age ≥ 18 years old
2. Positive SARS-CoV-2
3. Admitted to an acute care facility
4. Informed consent able to be provided by the patient or healthcare proxy
5. Severe or life-threatening disease defined by at least one of the following: Respiratory rate ≥ 30/min, oxygen saturation ≤ 93%, PaO_2/FiO_2 ratio < 300, lung infiltrates > 50% within 24-48 hours, respiratory failure, septic shock, OR multisystem organ failure

Instructions for providers located at https://team.myiuhealth.org/COVID-19

Convalescent plasma donation instructions: Patients that have recovered from COVID-19 (confirmed with positive SARS-CoV-2) can visit https://iuhealth.org/covid-19-recovered-plasma-donation-form to be evaluated for potential donation.

Corticosteroids: In general, steroids should be AVOIDED as treatment for COVID-19. Prior studies assessing outcomes in patients receiving systemic steroids for infections due to SARS-CoV and MERS-CoV found a lack of efficacy and possible harm. Steroids may still be warranted for other medical conditions, including ARDS.

¥Tocilizumab inclusion criteria (must meet all criteria)

1. Positive SARS-CoV-2 test
2. Bilateral infiltrates on high flow nasal cannula OR mechanical ventilation
3. Hypotension requiring 1 pressor OR evidence of end organ failure
4. At least ≥ 1 of the following:
   a. Ferritin > 300 µg/L with doubling w/in 24hr
   b. Ferritin > 650 µg/L and LDH > 250 units/L
   c. D-dimer > 1000 ng/mL
   d. Serum IL-6 ≥ 3xULN (normal ≤ 5 pg/mL)
5. $Pa0_2/Fi0_2$ ≤ 200

Exclusion criteria: > 2 vasopressors and/or > 3 organ systems failing.

Consider ID consult for ICU patients and PCU patients with rapidly increasing 02 requirements **OR** immunocompromised patients (see below):

- Transplant
- HIV w CD4<200
- Active chemotherapy/neutropenia
- On biologics

Up-to-date drug interaction information can be found at the following link: http://www.covid19-druginteractions.org

IU Health AHC HCQ Literature Summary 4.22.2020
Prepared by Armisha Desai, PharmD BCPS, BCIDP

HCQ Studies -- Most studies listed are NOT peer reviewed										
Reference	**Study design**	**Number of pts**		**Treatment regimen**	**Severity of symptoms/ age**	**Endpoints**	**Outcomes**	**Outcome Summary**	**ADR reported**	**Limitations/Issues**
		HCQ	**Control**							
Chen et al. (1)	Unblinded, RCT - randomized to 1:1	n=15 HCQ + SOC	n=15 SOC	**HCQ** 400 mg daily x 5 day SOC not defined	Not defined in abstract	Primary endpoint: negative viral conversion rate on day 7	Negative PCR day 7: 86.7 % HCQ vs 93.3% SOC P>0.05	HCQ No benefit	Transient diarrhea/abnormal LFT P>0.05: - HCQ: 4 pts (26.7%) - SOC: 3 pts (20%)	Actually study NOT published in English; Did not define SOC; small sample size; not powered
Chen et al. (2)	Blinded RCT	n=31 HCQ + SOC	n=31 SOC	**HCQ:** 200 mg BID x 5 days **SOC:** oxygen, antiviral agents, antibacterial agents, IVIG, +/- corticosteroids	Mild disease: CT + Pna; $Sa0_2/SP0_2$ >93% OR P/F >300 mmHg; **Mean age 44.7 yo**	Primary endpoint: Time to clinical recovery (return of body temps and cough relief x >-72h) followed for 5 days OR first major ADR; CT on day 1 and day 6 to determine pulm recovery: exacerbated, unchanged, or improved	Fever duration: shorter in HCQ group 2.2 days vs 3.2 days Cough recovery: shorter in HCQ group 2 vs 3.1 days Progression to severe disease: 0 pts in HCQ vs 4 pts in SOC CT improved: 80.6% HCQ vs 54.8% SOC	HCQ benefit in symptoms and imaging	HCQ: -Rash - 1 pt -headache - 1 pt SOC: 0	Excluded severe renal failure (est crcl < 30 mL/min/1.73m^2) Small study; included younger patients; does not describe what agents in SOC patients receive - possibly bias/confounds results; not powered
Tang et al. (3)	Multicenter, randomized, parallel, open-label; Pts stratified into mild/moderate or severe, then randomly assigned 1:1	n=75 HCQ + SOC	n=75 SOC	**HCQ:** 1200 mg daily x 3 days, followed by 800 mg daily x 2-3 weeks **SOC:** could include other antivirals	99% "mild-moderate" and 1% "severe" (did not define) mean symptom onset 16 days prior to randomization **mean age: 46 yo**	Primary endpoint: negative conversion w/in 28 days Secondary endpoint: alleviation of clinical symptoms; lab parameters; and radiology imaging; Additional endpoints in severe cases -all cause mortality; clinical status; days of mechanical ventilation/ECMO/supplemental o2/hospital stay Additional endpoints in mild/moderate cases: disease progression	Primary endpoint: neg PCR at 28 days: 85.4% HCQ and 81.3% SOC Secondary endpoint: -Clinical symptom relief: 59.9% HCQ vs 66.6% SOC -Time to symptom relief: 19 days HCQ vs 21 days SOC -Lab parameters: recovered faster in HCQ vs SOC, but overall improvement was similar at 28 days -Disease progression: 2 pts in HCQ had disease progression vs 0 in SOC Post- hoc analysis: showed higher efficacy of alleviation of sym when other anti-viral agents were removed from both groups (n=14 in each arm; HR 8.83 95% CI 1.09-71.3)	No difference in PCR conversion or symptom relief. *Possible benefit if removed all pts on other antivirals*	HCQ: 21 pts (30%) had ADR vs 7 pts - most common ADR was diarrhea (10% HCQ vs 0% SOC) -1 pt HCQ blurred vision prompting d/c; -1 pt HCQ increased thirst - HCQ dose decreased;	Excluded severe liver or renal disease. Did not meet power (needed 180 pts per group); did not define mild/moderate OR severe; 79% of patients had concomitant medications before randomization (unsure what meds..)?; didn't discuss what SOC options pts received; much higher and longer duration of HCQ; average symptom onset prior to enrollment 16 days

Mahevas et al. (4)	Retrosp. Study w propensity score	n=84 HCQ	n=97	**HCQ** 600 mg daily in first 48h of admission **SOC**: No HCQ w/in 48h of admission (8 pts did get HCQ >48h)	Require supplemental 02 >=2 L **mean age: 60 yo**	Primary outcome: Composite transfer to ICU within 7 days of inclusion/death from any cause. Secondary outcome: All-cause mortality at day 7; ARDS; -All pts had 12 lead ECG at baseline and day 3-5 -End of follow up 7 days post randomization, OR discharge home, OR death	Primary outcome: transfer to ICU/death 20.5% HCQ (n=16) vs 22.1% No HCQ (n=21) (RR0.93 95% CI 0.48- 1.81) Secondary outcomes: Death 2.8% HCQ (n=3) vs 4.6% (n=4) (RR 1.15 95% CI 0.66-2.01); ARDS 22.7% HCQ (n=24) vs No HCQ 24.1% (n=23) (RR 1.15 95%CI 0.66-2.01) *used weighted proportions*	No benefit w HCQ	HCQ: 8pts (9.5%) ECG modifications req HCQ d/c at median 4 days - 7 QTc >60 ms and 1pt > 500 ms ; -1 pt developed 1st degree AV block. No HCQ arm: 1 pt developed L bundle branch block on day 8 (had HCQ on day 5 of hospitalization + Lopinavir/ritonavir). Of note: 17 pts (20%) in HCQ also received azith	Excluded ESRD; organ failure req immediate admission to ICU/CCU; ARDS on admission; other COVID meds within 48hrs from admission; Excluded confusion at admission, CKD, HF and liver cirrhosis from final PS due to >10% difference btw groups; 8 pts in the HCQ arm did receive HCQ after the 48h enrollment window. Safety endpoint Qtc - 17 pts in HCQ also had azithro, no mention of azithro use in non HCQ arm or % of ECG changes in HCQ there were also on azithro
Gautret et al. (5)	Open label-non randomized	n=20 HCQ (excluded 6 pts?)	n=16	**HCQ** 200 mg TID x 10 days **Control:** pts that refused HCQ OR at centers w/o HCQ	Grouped: asymptomatic (16.7%), URTI (61.1%), LRTI (22.2%) **mean age 45 years; but HCQ 51.2 yo vs no HCQ 37.3yo**	Primary outcome: virological clearance at day 6 post-inclusion. Secondary outcome: Virologic clearance overtime, clinical f/u (temp, RR, LOS, mortality), SE	Primary outcome: 70% HCQ negative PCR vs 12.5% control (p=0.001); - Subset of HCQ + Azith (6pts) 100% neg PCR at day 6 vs 57.1% in HCQ alone	HCQ +/- azithro arm had higher viral clearance	Didn't comment, although listed as secondary endpoint?	Excluded pts w G6PD and QT prolongation (did not specify). Excluded 6 pts in HCQ group due to 3 pts moving to ICU, 1 pt died, 1 pt d/c from hospital, 1 pt d/c med due to nausea; use a PCR CT threshold of >=35 to be considered negative (standard?); Control arm - 5/16 did not have PCR done on day 6 --lead them to count as PCR POSITIVE vs only 1/20 in HCQ group; didn't comment on SE; statistical analysis questions
Gautret et al. (6)	Observational study	n=80 HCQ+ Azithr	none	**HCQ** 200 mg TID x 10 days + Azithro 500 mg x 1, 250 mg daily x 4 days (Treatment d/c or not started if QTc >500ms)	URTI (41.2%); LRTI (53.8%); asymptomatic (5%); 92% low NEWS score **Median age: 52 yo**	Primary endpoint: clinical course req o2 therapy or transfer to ICU after at least 3 days of treatment; contagiousness defined by PCR CT<34; LOS	Primary outcome: 15% req o2; 3.8% pts transferred to ICU; 1.2% pt died. -83% had neg PCR at day 7, 93% negative at day 8; CT >34 in all pts by day 12 -81% pts "favorable outcome and d/c w low NEWS score (93.8%)	HCQ + azithro: "neg" PCR by day 12	HCQ + Azithro: -N/V 2.5% - diarrhea 5% -blurred vision 1.2%	No control group; Included 6 pts in previous trial; neg PCR = CT >= 35 (standard?); observational study; NEWS scores didn't change (low risk pts)
Molina et al. (7)	Observational study	n=11 HCQ+ Azith	none	**HCQ** 600 mg daily x 10 days + azithromycin 500 mg x 1, 250 mg daily x 4 days	10/11 pts had fever and on O2 at initiation **mean age: 58.7yo**	Primary endpoint: COVID PCR negative at day 5	Primary outcome: 20 pts (2/10) had neg PCR at day 5. -1 pt died (no f/u PCR) - 2 transferred to ICU	HCQ+ Azith no benefit	1 pt d/c due to QTc prolongation (405 to 470 ms) - d/c day 4 of therapy	11 pt sample only. No control

Esper et al. (8)	Prospective, open label-Non-Randomized	n=412 HCQ +Azith	n=224	**HCQ** 800 mg x 1 day, 400 mg daily x 6 days + azithromycin 500 mg daily x 5 days	Outpts via telemedicine clinic w >3 days of flu-like symptoms; **Mean age 62.5 yo**	Primary endpoint: Need for hospitalization (worsening general condition OR O2<90%)	Primary Endpoint: HCQ group 1.9% required hospitalization vs 5.4% in control group (P<0.0001) -NNT=28 pts to prevent 1 hospitalization - If treated before 7 days of symptom onset, had a lower rate of hospitalization compared to when txt started >7 days *More pts w DM in HCQ arm; More pts w s/s flu-like illness in HCQ arm*	HCQ+azithro decreased need for hospitalization	HCQ + Azithro: - diarrhea 69 pt (16.5%) -nausea 31 pts (16.5%) -dizziness 9 pts (1.94%) -vomiting 5 pt (1.21%) -allergy 4pts (0.97%) -visual disturbances 1pt (0.24%) -2 deaths in treatment group; 1 pt ACS and 1 pt metastatic cancer - neither thought to be related to study drugs by author Control arm: not reported	In Dropbox (not even pre-peer reviewed…maybe IRB issue?); Not mandatory to get COVID + PCR (diagnosis based on symptoms? so might have been something else?); Did not specify follow up QTc or initial QTc recordings; excluded severe renal failure, known QT prolongation, severe liver disease; no power analysis done; did not comment on ADR in control group
Magagnoli et al. (9)	Retrospective cohort study in VA hospitals	n=97 HCQ; n=113 HCQ + Azith	No HCQ n= 158	HCQ; HCQ + Azith; No HCQ No doses/duration listed**	All inpatients meeting inclusion criteria (COVID +; complete data including: BMI, vitals, d/c dispo status); **Median age >60 yo**	Outcomes: Death or discharge, requiring ventilation, and "results of pts requiring vent"	Deaths: HCQ 27.8%; HCQ + azith 22.1%; No HCQ 11.4% Mechanical ventilation: HCQ 13.3%; HCQ+Azith 6.9%; No HCQ 14.1% Propensity matched analysis: "compared to no HCQ group, there was a higher risk of death from any cause in the HCQ group (HR 2.61, 95% CI 1.1-6.17; p=0.03) but NOT in the HCQ + azith group (HR 1.14, 95% CI0.56-2.32; P=0.75) -No difference in any group regarding mortality in those requiring ventilation	Possible increase in death in HCQ group vs no HCQ group, but NOT in HCQ + Azithro group	Did not discuss ADR	Only included males. Retrospective study, treatment arms vary in severity of illness and comorbiditites, with HCQ +/- azith having more comorbidities AND being more hypoxic w 02<94% (37% HCQ; 42.5% HCQ+azith; 27% no HCQ) , authors tried to adjust for this with PS including "all covariates" -but did not provide any data/stats on PS matching. No ADR reported. No doses/duration listed for HCQ +/- azithromycin

Assessing QTc Prolongation

Reference	Study design	Number of pts	Control	Treatment regimen	Patient type	Primary outcome	Outcome
Chorin et al. (10)	Retrospective, observational study	n=84	none	HCQ + Azith - - no doses mentioned	COVID +	Describe Qtc prolongation in pts w HCQ and azithromycin in NY	84 pts w combined HCQ and azithromycin: 4 died of MOF (no arrhythmias); 0 pts had TdP; Pre QTc 435ms to Post Qtc 463 ms; 11% developed Qtc >500 ms - Multivariate analysis development of acute renal failure was significant predictor of severe QTc prolongation

Lane et al. (11)	review of literature to determine ARD of HCQ +/- Azith	HCQ: n=956,374 HCQ + AZT: n=323,122 HCQ + AMX: n= 351,956	n=310, 350 (SSZ)	HCQ vs SSZ; HCQ + Azith vs HCQ + Amox	RA and non RA patients	New user cohort studies used to estimate safety of HCQ compared to sulfasalazine and to assess the risk associated w addition of AZM compared to amoxicillin in HCQ users in pts w RA	Initial 1 month of HCQ showed no excess risk of any considered safety outcomes compared to equivalent therapy (SSZ); 1 month use of HCQ + AZM had 15-20 % increase risk of angina/chest pain and HF and 2 fold increase risk of cardiovascular mortality

References:

1. http://www.google.com/url?sa=t&rct=j&q=&esrc=s&source=web&cd=1&cad=rja&uact=8&ved=2ahUKEwiMzMiOhfDoAhXbVc0KHRFWBsUQFjAAegQIARAB&url=http%3A%2F%2Fwww.zjujournals.com%2Fmed%2FEN%2F10.3785%2Fj.issn.1008-9292.2020.03.03&usg=AOvVaw1GDCr79UTznuYRjrdVozbJ
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