Indiana University Health

Updated 5/6/2020
Endorsed by IUHP AHC Infectious Diseases Physicians and ID Pharmacy

Indiana University ADULT AHC Inpatient Management of Confirmed SARS-CoV-2 (COVID19)

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
SpO2 >94% on room air WITH OR WITHOUT radiographic evidence of pneumonia

May be eligible for Remdesivir Moderate Study. Proceed unless contacted by study coordinator.*

If patient does not meet criteria or is unable to enroll:
Supportive Care

Recommended labs for mild/moderate disease:
Daily x 72 hours: CBC w/diff, CMP, CK, CRP, LDH, Ferritin, D-dimer

Moderate Disease
SpO2 ≤94% on room air WITH OR WITHOUT radiographic evidence of pneumonia

May be eligible for Remdesivir Severe Study OR TJ003234 Study. Proceed unless contacted by study coordinator.*

If patient is not enrolled:
Assess for eligibility for convalescent plasma≠
If your patient may be eligible, consult ID for further assessment and instructions

If patient does not meet criteria:
Supportive Care‡

Severe Disease
SpO2 <94%, RR ≥ 30 breaths/min, PaO2/FiO2 ≤ 300 mmHg OR mechanical ventilation

May be eligible for Remdesivir Severe Study OR TJ003234 Study. Proceed unless contacted by study coordinator.*

If patient is not enrolled:
Assess for eligibility for convalescent plasma≠
If your patient may be eligible, consult ID for further assessment and instructions

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

AAHC IUH COVID Therapies

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.

Remdesivir*: Antiviral – IUH enrolling patients in the Moderate and Severe arms. Patients may not receive tocilizumab before or after enrollment. Patients may receive convalescent plasma after remdesivir has been completed.

TJ003234*: IUH enrolling patients into Phase 1b/2 study for Severe Coronavirus. Patients may not receive convalescent plasma before enrollment, but may for salvage afterward. Patients may receive tocilizumab ≥24hrs prior to enrollment, but not afterward.

*Due to high demand and limited drug supply, study coordinators are randomly selecting patients who meet inclusion criteria and will approach patients for inclusion independently of ID consultation or primary team request.

≠Convalescent plasma inclusion criteria (must meet all 5)

1. Age ≥ 18 years old
2. Positive SARS-CoV-2 test
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%, PaO2/FiO2 ratio <300, lung infiltrates >50% within 24-48hrs, respiratory failure, septic shock, OR multisystem organ failure

Exclusion criteria: Enrolled in Remdesivir or TJ003234 Study.

‡Hydroxychloroquine We have considered recent pre-print studies and judged the risk of hydroxychloroquine to outweigh the possible benefits, and **no longer recommend** its use. See attached chart for a summary of literature. If through the shared decision-making process, a patient or their healthcare proxy wish to pursue treatment with hydroxychloroquine, most commonly studied dose is: 400mg po bid x2 doses, then 400mg po qday for 4 doses.

Safety recommendations:
Send β-HCG if of childbearing potential, baseline EKG, review medication list for QTc-prolonging medications. Do not use HCQ if baseline QTc >500 ms.
Lab monitoring - Recommend daily K and Mg. Keep K ≥4.0 mEq/L, Mg≥1.5 mEq/L.
If discharged prior to completing inpatient hydroxychloroquine regimen, repeat EKG prior to discharge.

¥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 >650µg/L and LDH>250
   c. D-dimer >1000 ng/mL
   d. Serum IL-6 ≥3xULN
5. $Pa0_2/Fi0_2$ ≤200

Exclusion criteria: >2 vasopressors, >3 organ systems failing, enrolled in TJ003234 Study or concurrent remdesivir use

ID Consult will be automatic for ICU patients.
ID consult recommended for PCU patients with rapidly increasing 02 requirements **OR** immunocompromised patients (transplant, HIV w/ CD4<200, active chemotherapy/neutropenia, on biologics

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

Mallat et al (10)	Retrospective observational study	n= 21 HCQ	n=13 No HCQ	HCQ: 400 mg BID x 1 day, 400 mg daily x 10 days	All pts meeting inclusion criteria (≥18 yo,COVID19); Mild cases-only 6 pts req 0_2 w NC (2-4l/min) **Median age 37 yo**	Primary endpoint: Time to SARS-CoV-2 negativity test (2 negative PCR obtained 24 hrs apart)	Primary endpoint: HCQ 17 days to neg PCR vs No HCQ 10 days (p=0.023) -Multivariate regression analysis, HCQ associated w longer time to neg PCR -Median time of symptoms to HCQ =4 days -14 pts had pneumonia -Higher comorbidities and D-dimer levels in non-HCQ	HCQ arm had slower time to viral clearance by neg PCR	Reported no side effect	No power analysis performed; small sample size; did not discuss other therapies (such as steroids) that could prolong viral shedding; did not discuss when repeat PCRs were done
Yu et al. (11)	Retrospective study	n=48 HCQ	n=520 "Basic txt" - NHCQ	HCQ: 200 mg BID x 7-10 days	Critically Ill – needing mech ventilation OR having septic shock OR organ failure requiring ICU admission **Median age 68 yo**	Primary endpoint: In hospital death; LOS; IL-6 levels	Primary outcome: Mortality: 9/48 (18.8%) HCQ vs 238/520 (45.8%) NHCQ; p<0.001) LOS: 32 days HCQ vs 30 days NHCQ; p=0.098; -Hospital LOS until death 15 days HCQ vs 8 days NHCQ; p=0.021 -COX regression HCQ associated with decreased mortality (HR 0.32; 95% CI 0.16-0.62; p<0.001) IL-6: Post IL-6 levels in HCQ sig decreased from pre-levels (22.2 vs 5.2 pg/mL p=0.002) vs NHCQ (21.3 vs 20.2pg/mL p>0.05). However, IL-6 levels increased in HCQ once therapy was done.	Lower mortality in HCQ group	Not reported	No power analysis; retrospective (? Only 48 pts had HCQ?); both groups received similar additional antivirals (including lopinavir/ritonavir; entecavir; ribavirin), IVIG, "immunoenhancers"; ABX and interferon were higher in NHCQ group; No severity score (APACHE/SOFA) score on patients -- unclear if each group had similar severities

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
2. https://www.medrxiv.org/content/10.1101/2020.03.22.20040758v3
3. https://www.medrxiv.org/content/10.1101/2020.04.10.20060558v1
4. https://www.medrxiv.org/content/10.1101/2020.04.10.20060699v1
5. https://www.sciencedirect.com/science/article/pii/S0924857920300996?via%3Dihub
6. https://www.sciencedirect.com/science/article/pii/S1477893920301319
7. https://doi.org/10.1016/j.medmal.2020.03.006
8. https://pgibertie.files.wordpress.com/2020/04/2020.04.15-journal-manuscript-final.pdf
9. https://www.medrxiv.org/content/10.1101/2020.04.16.20065920v1.full.pdf
10. https://www.medrxiv.org/content/10.1101/2020.04.02.20047050v1
11. https://www.medrxiv.org/content/10.1101/2020.04.08.20054551v1