COVID-19 Update
3/23/2020

Clinical Case

Patient 1

- 49 year old male with a travel hx to Texas on March 1
- March 6 presents with cough and fever and goes to work
- March 9 presents to ED and sent home with antibiotics
- March 10 Admitted with CAP
- March 11 in ICU on vent critically ill (COVID +)

Questions

- What are the recommendations for health care workers who develop fever or respiratory symptoms?
- Who should be quarantined?

Clinical Case

Patient 2

- 73 year old female admitted to ICU with pneumonia
- CT: Bilateral ground glass opacities
- Labs: WBC 12.6 x 10^3 /mcL, Absolute lymphocytes 871
- AST 70 IU/mL, ALT 91 IU/mL
- Otherwise normal (COVID pending)

Question?

- Any signs of COVID?
- Treatment?

Characteristics and Outcomes of 21 Critically Ill Patients With COVID-19 in Washington State

- Patients admitted to the ICU in Evergreen Hospital with a positive NP COVID PCR between February 20 and March 5, 2020.
- 21 cases Included
- Mean age 70 (43-92), 52% Male
- Comorbidities identified in 86%
  - CKD and CHF most common
- Mean onset of symptom before presenting to the ICU was 3.5 days
- 81% were admitted to the ICU less than 24 hours after hospital admission

JAMA. Published online March 19, 2020. doi:10.1001/jama.2020.4326

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- Mean onset of symptom before presenting to the ICU was 3.5 days
- 81% were admitted to the ICU less than 24 hours after admission
- 95% abnormal x ray on admission

Admission symptoms	
Cough	11 (47.6)
Shortness of breath	17 (76.2)
Fever[c]	11 (52.4)
Temperature (range), °C	37.6 (35.3-39.2)

Admission chest radiograph findings[d]	
Bilateral reticular nodular opacities	11 (52.4)
Ground-glass opacities	10 (47.6)
Pleural effusion	6 (28.6)
Peribronchial thickening	5 (23.8)
Pleural effusion	5 (23.8)
Focal consolidation	4 (19.0)
Pulmonary edema	2 (9.5)
Venous congestion	1 (4.8)
Atelectasis	1 (4.8)
Clear	1 (4.8)

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Characteristics and Outcomes of 21 Critically Ill Patients With COVID-19 in Washington State

- 14/21 (67%) Normal WBC
- 14/21 (67%) Lymphocyte count of < 1000 cell/uL
- 38% Abnormal LFT's

Admission laboratory measures, mean (range)[a]		
White blood cell count, /μL	9365 (2890-16 900)	4000-11 000
Absolute lymphocyte count, /μL	889 (200-2390)	1000-3400
Hemoglobin, g/dL	11.4 (8.0-13.7)	11.2-15.7
Platelet count, $\times 10^3$/μL	215 (52-395)	182-369
Sodium, mmol/L	137 (125-148)	135-145
Creatinine, mg/dL	1.45 (0.1-4.5)	0.6-1.2
Total bilirubin, mg/dL	0.6 (0.2-1.1)	0-1.5
Alkaline phosphatase, U/L	80 (41-164)	31-120
Aspartate aminotransferase, U/L[e]	273 (14-4432)	5-40
Alanine aminotransferase, U/L[e]	108 (11-1414)	5-50
Creatinine kinase, U/L	95 (45-1290)	21-215
Venous lactate, mmol/L	1.8 (0.8-4.9)	<1.9
Had troponin level >0.3 ng/mL, No. (%)	3 (14.0)	
Brain-type natriuretic peptide, pg/mL	4720 (69-33 423)	<450
Procalcitonin, ng/mL	1.8 (0.12-9.56)	0.15-2.0

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Characteristics and Outcomes of 21 Critically Ill Patients With COVID-19 in Washington State

- 15/21 (71%) required mechanical ventilation
  - 100 % had ARDS
    - 53% had severe ARDS by 72 hs
- 14/21 (68%) required vasopressors

Use of vasopressors	14 (67.0)
Absolute lymphocyte count at nadir (range), /μL	525 (180-1100)
Evidence of co-infection[c]	
Bacterial	1 (4.8)
Viral	3 (14.3)
Acute kidney failure[d]	4 (19.1)
Cardiomyopathy[e]	7 (33.3)
Acute hepatic injury[f]	3 (14.3)
Seizures	1 (4.8)
Length of follow-up, mean (range), d	5.2 (1-10)

Outcomes (As of March 17,2020)	
Died	11 (52.4)
Survived to transfer out of ICU	2 (9.5)
Remains critically ill and requires mechanical ventilation	8 (38.1)
Length of follow-up for those who survived or remain critically ill, mean (range), d	7.5 (5-10)

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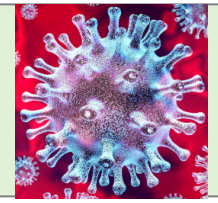
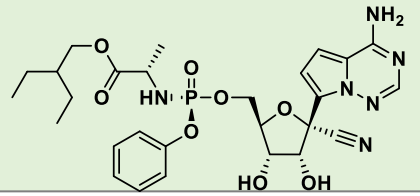
Remdesivir Activity, Administration, Pharmacology and Pharmacokinetics

- **In vitro activity against an array of RNA virus families including:**
  - *Filoviridae, Paramyxoviridae, Pneumoviridae,* and *Coronaviridae*



- **Intravenous administration once daily via 30 min infusion**
  - Loading dose is Remdesivir 200mg
  - Maintenance dose is Remdesivir 100mg
  - Available in solution and lyophilized formulation

- Remdesivir is not suitable for oral administration due to almost complete first pass metabolism
- The $T_{1/2}$ of GS-443902 observed in vitro in human macrophages (11 hours) and in vivo in rhesus monkey PBMCs following IV administration (22 hours) supports once-daily dosing
- Metabolism is to be predominantly mediated by hydrolase activity
- Major routes of elimination include renal (74%) and biliary (18%)



Gilead Data on file
Sheahan TP, et al. Sci Transl Med 2017;9:eaal3653
Warren et al, 2016 Nature

Remdesivir (RDV, GS-5734)

- Some clinical trial data anticipated beginning-mid April
- Will soon be available through Expanded Access Program
  - Transitioning from Compassionate Use to Expanded Access Program
    - Removes the requirement to review each request on an individual basis
    - Should speed up the delivery of RDV to physicians treating severely ill patients who cannot take part in a trial
  - During the transition period, new compassionate use requests are not being accepted
    - Exceptions are made for pregnant women and those under 18 years of age

Lopinavir-ritonavir (Kaletra®)

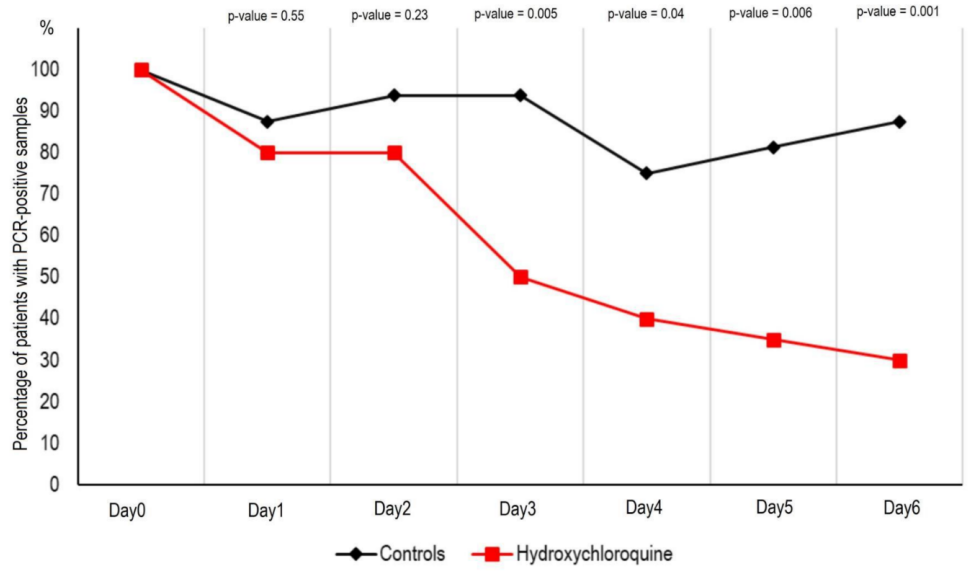
Manufacturer: Abbvie

- LOTUS China Trial
  - Randomized, controlled, open-label trial in adult patients hospitalized with COVID-19
  - Patients received lopinavir-ritonavir (400mg/100mg) twice a day for 14 days in addition to standard of care, or standard of care alone
  - Results
  - Lopinavir-ritonavir did not significantly accelerate clinical improvement, reduce mortality, or diminish throat viral RNA detectability in patients with serious COVID-19
    - Lopinavir-ritonavir patients did not differ in time to clinical improvement from that of patients assigned to standard of care (16 days vs 16 days) in the intention-to-treat populations
    - Percentage of patients with detectable viral RNA for SARS-CoV-2 was similar in both groups on any sampling day
    - Mortality was similar at 28 days in both groups (lopinavir-ritonavir 19.2% vs standard of care 25% [95% CI, -17.3 to 5.7])
    - ~14% of patients could not complete full 14-day course due to gastrointestinal adverse events

Hydroxychloroquine and COVID-19

- 26 Patients received hydroxychloroquine 200mg by mouth 3 times a day x 10 days +- azithromycin and 16 were control patients
- 6 hydroxychloroquine patients were lost in follow-up and none of the control patients were lost in follow-up
- Depending on their clinical situation, azithromycin was added to the treatment
- At day 6 post-inclusion, 70% of hydroxychloroquine-treated patients were virologicaly cured compared with 12.5% in the control group
- At day 6 post-inclusion, 100% of patients treated with hydroxychloroquine and azithromycin combination were virologicaly cured comparing with 57.1% in patients treated with hydroxychloroquine alone, and 12.5% in the control group

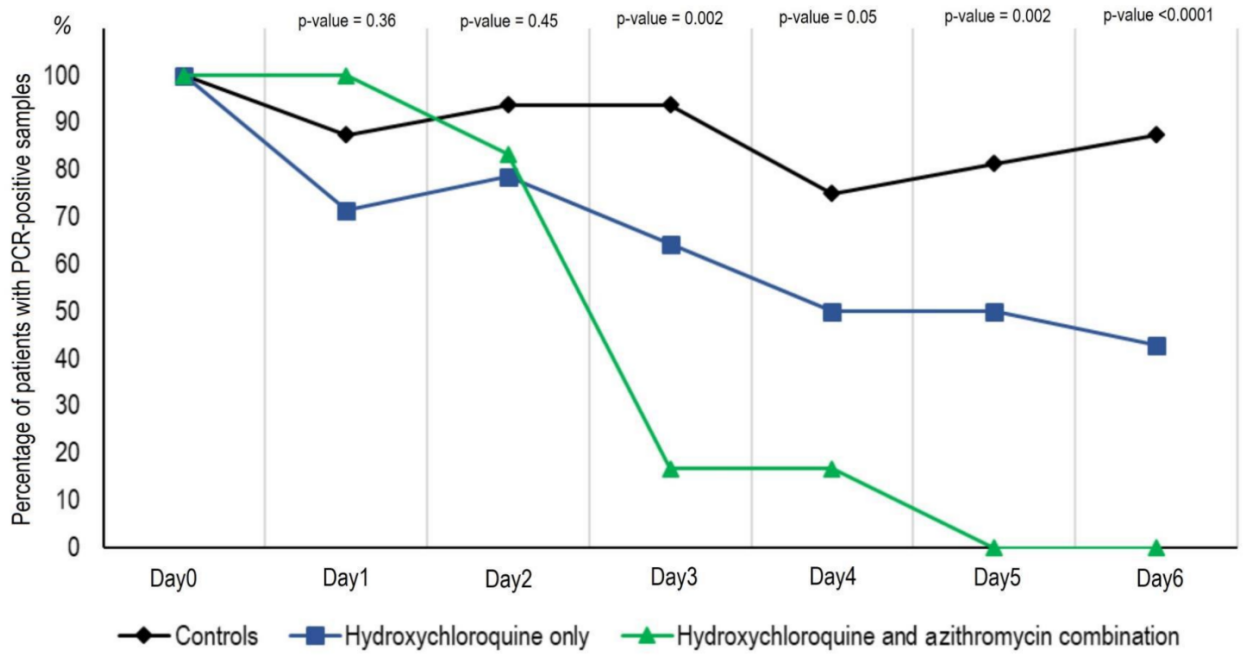
Figure 1. Percentage of patients with PCR-positive nasopharyngeal samples from inclusion to day6 post-inclusion in COVID-19 patients treated with hydroxychloroquine and in COVID-19 control patients.



Philipe Gautret, et al. International Journal of Antimicrobial Agents Online March 10, 2020

Hydroxychloroquine and COVID-19

Figure 2. Percentage of patients with PCR-positive nasopharyngeal samples from inclusion to day6 post-inclusion in COVID-19 patients treated with hydroxychloroquine only, in COVID-19 patients treated with hydroxychloroquine and azithomycin combination, and in COVID-19 control patients.



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- March 6 presents with cough and fever and goes to work
- March 9 presents to ED and sent home with antibiotics
- March 10 Admitted with CAP
- March 11 in ICU on vent critically ill (COVID +)

Questions

- What are the recommendations for health care workers who develop fever or respiratory symptoms?
  - DO NOT COME TO WORK!!!!!!!
- Who should be quarantined?
  - Anyone who was within a 6 feet distance for more than 10 minutes
  - Anyone who shared objects
  - Anyone who got coughed or sneezed on.

Clinical Case

Patient 2

- 73 year old female admitted to ICU with pneumonia
- CT: Bilateral ground glass opacities
- Labs: WBC 12.6 x 10^3 /mcL, Absolute lymphocytes 871
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- Otherwise normal (COVID pending)

Question?

- Any signs of COVID?
  - Lymphopenia
  - LFT elevation
  - Bilateral ground glass opacities
- Treatment?
  - Remdesevir expanded access program ?
  - Hydroxycholoroquine + Azythromycin ?