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## Coronavirus Disease 2019 (COVID-19)

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# CORONAVIRUS DISEASE 2019 (COVID-19)

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WHAT DO WE KNOW ABOUT  
COVID-19?

**NOTHING**



# OBJECTIVES

- Discuss epidemiology of SARS-CoV-2 and its relation to other coronaviruses
- Discuss route of transmission, period of infectivity, and possible immunity
- Review risk factors associated with severe illness and available methods for predicting mortality
- Review clinical presentation including symptomology, abnormal labs, and image findings
- Discuss overall course as well as complications that may develop for those infected
- Develop an understanding of management of a patient with COVID-19, including investigational agents currently being evaluated for use



# EPIDEMIOLOG Y



- Coronaviruses are widespread among birds and mammals
- Bats are host to the largest variety of genotypes
- 4 serotypes associated with disease in humans
  - HCoV-229E
  - HCoV-NL63
  - HCoV-C43
  - HCoV-HKU1
- Severe Acute Respiratory Syndrome (SARS-CoV)
  - 2002
- Middle Eastern Respiratory Syndrome (MERS-CoV)
  - 2012

Anthony SJ, et al. *Virus Evol.* 2017;1(3):012.  
*Quant ER. J Clin Microbiol.* 2010;48(8):



# EPIDEMIOLOG Y CONT.

- Coronavirus disease 2019 (COVID-19)
  - Betacoronavirus
  - Closely related to SARS-CoV, hence its name SARS-CoV-2
  - Bats are likely the primary source
- 2 types of SARS-CoV-2
  - L type
  - S type

Zhou P, et al. Nature. 2020;579(7789):270.  
Zhu N, et al. N Engl J Med. 2020;382(8):  
727.  
Tang Y, et al. National Science Review.



Thought to occur mainly via respiratory droplets



Can infect another individual if virus makes direct contact with mucous membranes



Or if an individual touches an infected surface and then touches his or her eyes, nose, or mouth

## ROUTE OF TRANSMISSION

Van Dorelmalen N, et al. N Engl J Med. 2020

# PERIOD OF INFECTIVITY

- Interval is uncertain
- Most of the information we have are from studies evaluating viral RNA detection
- Duration of viral shedding has also been found to be variable
  - In a study of 21 patients with mild illness, 90% had repeated negative viral RNA swabs 10 days after symptom onset
  - In another study of 137 patients, median viral shedding was 20 days (range of 8-37 days)



Zou L, et al. N Engl J Med. 2020;382(12):1177.  
Liu Y, et al. Lancet Infect Dis. 2020.



## PERIOD OF INFECTIVITY CONT.

- Rates of transmission from an individual with a symptomatic infection vary by location
  - China: 1-5% among >38,000 close contacts of confirmed COVID-19 patients
  - United States: 0.45% among 445 close contacts of 10 confirmed patients
- Transmission from asymptomatic individuals is still largely unknown
  - Singapore: 6.4%

Report of the WHO-China Joint Mission on Coronavirus Disease 2019 (COVID-19).  
Burke RM, et al. MMWR Morb Mortal Wkly Rep. 2020;69(9):245.





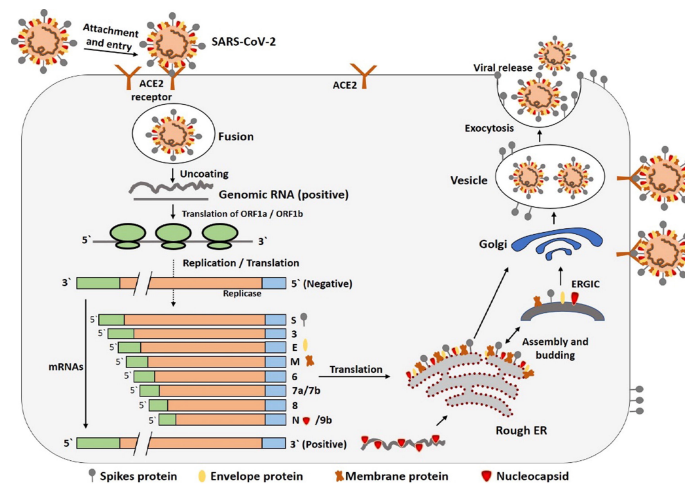
# IMMUNITY

- Antibodies are induced in those who have been infected
- Preliminary evidence suggests some of these antibodies may be protective
- Currently unknown how long protective immune response will last

To KK, et al. Lancet Infect Dis. 2020.



# LIFE CYCLE



Zhou F, et al. Lancet. 2020;395(10229):1054.



## SPECTRUM OF ILLNESS SEVERITY

- Report from Chinese Center for Disease Control and Prevention:
  - Mild: 81%
    - No or mild pneumonia
  - Severe: 14%
    - Dyspnea, hypoxia, or > 50% lung involvement on imaging within 24-48 hours
  - Critical: 5%
    - Respiratory failure, shock, multiorgan dysfunction



Wu Z and McGoogan JM, JAMA. 2020

Italy: 7.2%

South Korea: 0.9%

United States:  
1.1%

SPECTRUM  
OF  
ILLNESS  
SEVERITY  
CONT.

Grasselli G, et al. JAMA. 2020.  
KCDC. Updated on COVID-19 in Korea. 2020 Mar  
14.



## RISK FACTORS FOR SEVERE ILLNESS

- Severe illness can occur in health individuals of any age
- Primarily occurs in adults of advancing age or those with certain comorbid conditions:
  - Diabetes
  - Hypertension
  - Cardiovascular disease
  - Chronic lung disease
  - CKD
  - Cancer



Zhou F, et al. Lancet. 2020;395(10229):1054.

## RISK FACTORS FOR SEVERE ILLNESS CONT.

### 355 fatal cases in Italy

- Mean number of comorbidities was 2.7
- 3 patients had no underlying comorbidities

### Outbreak of COVID-19 in several long-term care facilities in Washington

- Median age was 83
- 94% had an underlying condition
- Hospitalization rate: 55%
- Fatality rate: 34%

Onder G, et al. JAMA. 2020.  
McMichael TM, et al. N Engl J Med. 2020.





# PREDICTING MORTALITY

- MuLBSTA Score

	No	Yes
Multilobe infiltrate	0	5
Absolute Lymphocyte count $<0.8 \times 10^9/L$	0	4
Bacterial infection	0	4
Smoking history	0	Prior: 2 3
Hypertension	0	2
Age $\geq 60$ years	0	2

Gou L, et al. Front Microbiol. 2019;10:2752



Acute kidney injury

Lymphopenia

Elevated liver enzymes

Elevated PT

Elevated troponin

Elevated D-dimer ( $>1$  mcg/mL)

PREDICTING  
MORTALITY  
CONT.

Zhou F, et al. Lancet. 2020;395(10229):1054.



# INITIAL PRESENTATION

Study of 138 patients in Wuhan:

Pneumonia seems to be the most frequent manifestation of infection, characterized by fever, cough, and fatigue

Fever: 99%	Fatigue: 70%	Dry Cough: 59%	Anorexia: 40%	Myalgias: 35%	Dyspnea: 31%	Sputum production: 27%
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Wang D, et al. JAMA. 2020.

## LAB AND IMAGE FINDINGS



- Lab findings:
  - Leukopenia or leukocytosis
  - Elevated aminotransferase
  - Elevated lactate dehydrogenase
  - Normal pro-calcitonin on admission
- Imaging:
  - CT chest showing bilateral ground-glass opacification

Wang D, et al. JAMA. 2020.

# COURSE AND COMPLICATIONS

Patients with initially mild symptoms may progress over the course of a week

- Study of 138 patients hospitalized in Wuhan:
  - Dyspnea: 5 days after symptom onset
  - Hospitalization: 7 days

Acute Respiratory Distress Syndrome (ARDS)

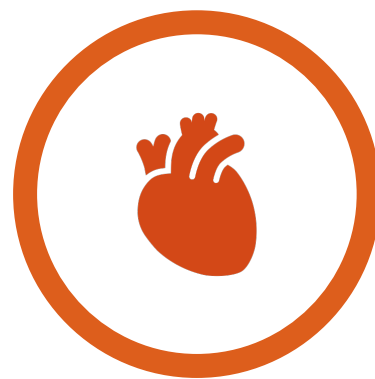
- Acute hypoxemic respiratory failure
- Can manifest quickly after onset of dyspnea
- 20% developed ARDS
- 12.3% required mechanical ventilation

Wang D, et al. JAMA. 2020.




# COURSE AND COMPLICATIONS CONT.

- Cardiac injury
  - Late complication
    - Arrhythmia
    - Pericarditis
    - Pericardial effusion
    - Cardiomyopathy
    - Sudden cardiac death
- Sepsis, shock, multi-organ failure appear to be uncommon
- WHO: recovery time is around 2 weeks for mild infections and 3-6 weeks for severe




Wang D, et al. JAMA. 2020.  
World Health Organization. 2020 Feb 24.






# MANAGEMENT

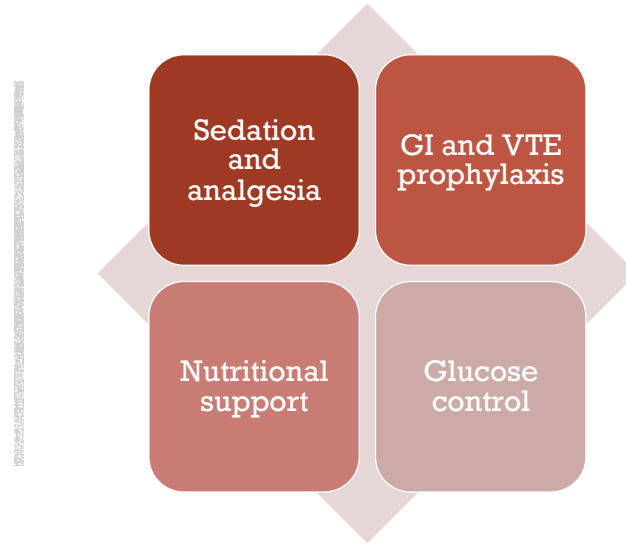
- Home care: appropriate for those with mild infection
  - Focuses on isolation and prevention of transmission to others
  - CDC recommendations:
    - Test-based strategy:
      - Resolution of fever
      - Improvement in respiratory symptoms
      - 2 consecutive negative nasopharyngeal swab specimens collected > 24 hours apart
    - Non-test-based strategy:
      - ≥ 7 days since symptom onset
      - ≥ 72 hours since symptom recovery

CDC. Disposition of non-hospitalized patients with COVID-19. 2020 Mar 16. 

- Hospital care
  - Supportive care and infection control
  - WHO recommends standard, contact, and droplet precautions with eye and face protection
  - Patients with severe disease often need oxygenation
    - SpO<sub>2</sub> ≥ 90%
    - Use of low-flow oxygen systems via nasal cannula (up to 6L/min)
    - Next steps are controversial and appear to be on a case by case basis:
      - High-flow vs early intubation

# MANAGEMENT CONT.

Anesi GL, et al. UpToDate. 2020 Apr 4. 



Anesi GL, et al. UpToDate. 2020 Apr 4.

## CHLOROQUINE AND HYDROXYCHLOROQUINE

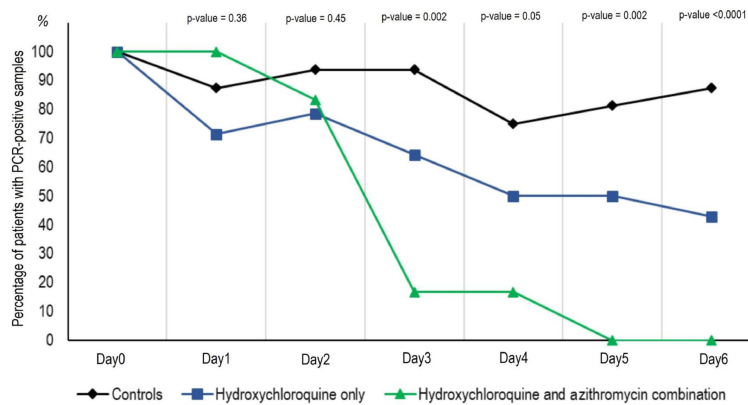
**Demonstrated  
in vitro  
activity  
against SARS-  
CoV-2**

- Proposed mechanisms:
  - Weak bases that raise pH of organelles essential for membrane fusion and subsequent release of virions
  - Inhibit entry through glycosylation of ACE2

Yao X, et al. Clin Infect Dis. 2020.



# CHLOROQUINE AND HYDROXYCHLOROQUINE CONT.



Philippe G, et al. Int J Antimicrob Agents. 2020.

# CHLOROQUINE AND HYDROXYCHLOROQUINE CONT.

- Chloroquine included in treatment guidelines from China's National Health Commission
  - Reported to be associated with reduced disease progression and duration of symptoms
- Possible toxicity
  - QTc prolongation
  - Cardiomyopathy
  - Retinal toxicity
- Optimal dosing unknown (hydroxychloroquine):
  - 400 mg BID on day 1, then 400 mg daily for 5 days
  - 400 mg BID on day 1, then 200 mg BID for 5 days
  - 600 mg BID on day 1, then 400 mg daily for 4 days
  - FDA: 800 mg on day 1, then 400 mg daily for 4-7 days

Yao X, et al. Clin Infect Dis. 2020.

# REMEDESIVIR

- Novel nucleotide analogue
- Demonstrated in vitro activity against SARS-CoV-2
- Proposed mechanism:
  - Inhibition of RNA-dependent RNA polymerase
- Several clinical trials are ongoing to evaluate efficacy
- Compassionate use for pregnant women and children
- IV: 200 mg as a single dose on day 1, then 100 mg daily for 5-10 days



Gilead Sciences Statement on the Company's Ongoing Response to the 2019 Novel Coronavirus (2019-nCoV). 2020 Jan.  
Agostini ML, et al. mBio. 2018 Mar;9(2).




# LOPINAVIR- ROTINAVIR

- Protease inhibitor
- Primarily used in the treatment of HIV
- Found to have no role in treatment
- Randomized trial of 199 patients with severe disease
  - No difference in time to clinical improvement or mortality at 28 days




Cao B, et al. N Engl J Med. 2020.




## CONVALESCENT PLASMA

- Collected from individuals who have recovered
- May contain antibodies to SARS-CoV-2
- Case series in Shenzhen, China:
  - 5 patients
  - Decreased nasopharyngeal viral load and improved oxygenation 12 days post transfusion
- FDA is accepting emergency new drug applications for patients with severe disease

Shen C, et al. JAMA. 2020. 

## SUMMARY

- Patients who are suspected for COVID-19 infection often present with symptoms consistent with viral pneumonia
- Progression of mild to severe disease can happen rapidly and is usually associated with dyspnea requiring oxygenation therapy
- For now, diagnosis and effective triage of patients is based on severity of symptoms in addition to abnormal imaging and laboratory findings
- Management of those with confirmed or suspected COVID-19 focuses on supportive treatment
- There are several investigational therapies currently being explored as possible antiviral treatment for COVID-19, however their efficacy is still unknown





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**THANK YOU!**

**QUESTIONS?**

