MHIF FEATURE:

Emergency Use of the Hemolung Device

CONDITION:	MD:	RESEARCH CONTACT:	MANUFACTURER:
Emergency Use of ECCO2R	Romiro Saavedra-Romero, MD	Kari Williams kari.Williams@allina.com Carina Benson carina.benson@allina.com	ALung Technologies, Inc.

DESCRIPTION:

As we are preparing for a potential surge in ICU patients as COVID-19 penetrates the community, it is our hope that extracorporeal carbon dioxide removal (ECCO2R) could be use in any hypercapnic respiratory failure syndrome and in patients with acute respiratory distress syndrome (ARDS) to facilitate instituting lung protective ventilation.

CONSIDERATION TO USE ECCO2R MAY BE:

- pH <7.20 from hypercapnia, and/or
- Plateau pressure >30 cm H20 or driving pressure >15 cm H2) despite optimization of mechanical ventilation.

MHIF Research Shared at Virtual ACC 2020

50 Total Presentations
- 32 Poster board Abstracts
- 7 Moderated or Oral Abstracts
- 11 Talks and Podium Presentations

66 MHIF/MHI Physician, Fellows, & Staff
- 31 MHI Physicians
- 5 Clinical Fellows and Residents
- 13 MHIF Staff Members
- 8 International Scholars
- 7 MHIF Interns
- 2 Allina Staff Members

A Perspective on the Chinese Experience with COVID-19

Yu Du, M.D.
Minneapolis Heart Institute Foundation, Abbott Northwestern Hospital
Dept. of Cardiology, Beijing Anzhen Hospital, Capital Medical University

Disclosures

- For educational and reference purposes only
- Recommendations on COVID-19 Management mainly on a basis of

Chinese Clinical Guidance for COVID-19 Pneumonia Diagnosis and Treatment (7th edition)

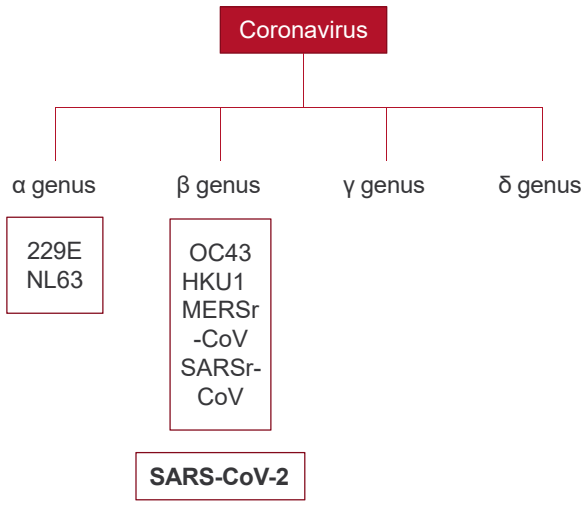
published by China National Health Commission on March 4, 2020

Outline

- What is the coronavirus disease 2019 (COVID-19)?
- How to prevent & identify COVID-19 infection?
- How to control COVID-19 pandemic?
- How to manage patients with COVID-19?
- COVID-19 & Cardiovascular Disease

COVID-19: SARS-CoV-2

- A cluster of cases of pneumonia with unknown etiology in Wuhan, China
- SARS-CoV-2, a novel coronavirus, leading to coronavirus disease 2019 (COVID-19)
- Coronavirus β genus, shares 96% homology with SARS-like coronavirus strain (BatCov RaTG13)

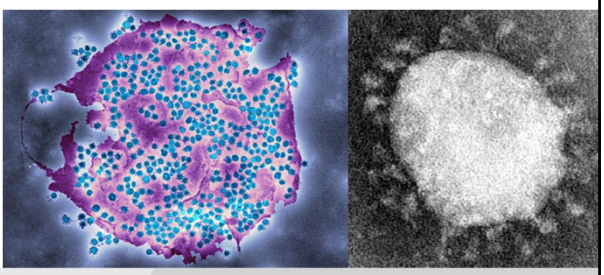


SARS, severe acute respiratory syndrome
MERS, Middle East respiratory syndrome

COVID-19: SARS-CoV-2

- Medium-sized enveloped positive-stranded RNA viruse
- Crown-like particles observed under transmission electron microscope (TEM)
- Origin: most probably from natural selection
- Fragile to ultraviolet and heat (56 ℃ for 30 min)

  Inactivated by liposoluble solvents

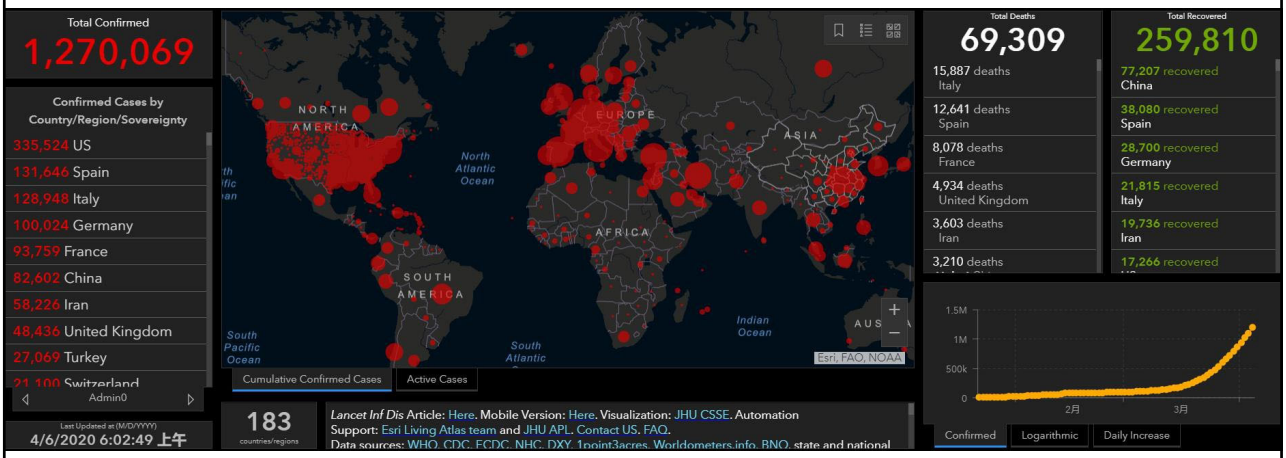


SARS, severe acute respiratory syndrome
MERS, Middle East respiratory syndrome

Andersen, K.G. et al. Nat Med (2020)

COVID-19: Geographic Distribution

by April-6-2020 17:37



https://coronavirus.jhu.edu/map.html

COVID-19: Epidemiology

- **Source of infection**

  Infected patients (symptomatic or asymptomatic)

- **Route of transmission**

  Respiratory droplets and close contact

  Aerosol transmission: plausible (high concentration, closed environment, & long time)

  Fecal-oral transmission (virus detected: saliva, urine & stool)

- **Susceptible population**

  Human beings are generally susceptible !!!

COVID-19: Clinical Manifestation

- **Incubation period:** 1-14 days following exposure (predominately 4~5 days)
- **Common symptoms:** fever (44% on admission [36.7-38.0 ℃], 89% during hospitalization [37.8-38.9 ℃]), dry cough & fatigue
- **Clinical classification**

  No/Mild/moderate (81%): no or mild pneumonia

  Severe (14%): dyspnea, hypoxemia, >50% lung involvement within 1~2 days

  Critical severe (5%): respiratory failure, shock, multi-organ dysfunction

- **Prognosis:** generally good, elderly and those with chronic comorbidities are relatively worse

  case fatality rate ranges from 5.8% (Wuhan) ~ 0.7% (rest of China), overall 2.3%

Wu Z, et al. JAMA. 2020 Feb 24.
Guan WJ, et al. N Engl J Med. 2020 Feb 28.

COVID-19: Differential diagnosis

- **COVID-19 mild type**

  Upper respiratory tract infections by other virus

- **COVID-19 pneumonia**

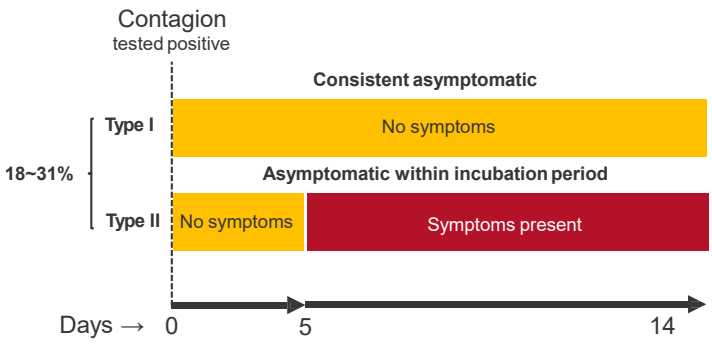
  Other known viral or mycoplasma pneumonia infections

- **Other non-infectious disease**

  eg. vasculitis, dermatomyositis, & organizing pneumonia

Nucleic acid test recommend:
Suspected cases, even common respiratory pathogen tested positive (co-infection)

COVID-19: Asymptomatic Infection Matters



CT imaging findings
50% (12/24) had patchy/ground-glass opacities
20% (5/24) had atypical imaging

Hu Z, et al. Sci China Life Sci. 2020 Mar 4.

Viral Shedding
Viral load detected in asymptomatic patients, similar to that in symptomatic patients

Zou L, et al. NEJM. 2020 Mar 19;382(12):1177-1179.

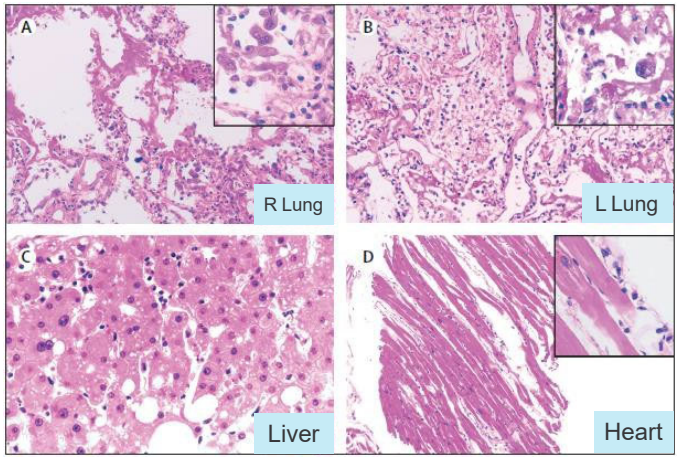
COVID-19: Autopsy

85 y/o, male, died of COVID-19 & pulmonary failure, autopsy<12 hrs

① Pleural thickening, adhesion (R)
② White patchy lesion (L)
③ White viscous fluid overflow, fiber bands
④ White foam mucus in the trachea
⑤ Gelatinous mucus attachment in the R lung bronchus
⑥ Yellow clear liquid in the pericardial cavity
⑦ Myocardial section is gray red fish like
⑧ Segmental dilatation & stenosis of small intestine alternate

Liu Q et al. Fa Yi Xue Za Zhi. 2020 Feb 25;36(1):21-23.

COVID-19: Pathology



- Fig. A, B: bilateral diffuse alveolar damage with cellular fibromyxoid exudates, interstitial mononuclear inflammatory infiltrates (lymphocytes)
- Fig. A: desquamation of pneumocytes and hyaline membrane formation (ARDS)
- Fig. C: microvesicular steatosis
- Fig. D: interstitial mononuclear inflammation

Xu Z, et al. Lancet Respir Med. 2020 Feb 18

ARDS, adult respiratory distress syndrome

COVID-19: Lab-routine Examination

- **Early stage:** leukocytes - / ↓, lymphocyte ↓
- **Most patients:** CRP ↑, ESR ↑, Procalcitonin -
- **Severe patients:** D-dimer ↑↑, lymphocyte ↓↓↓, inflammatory biomarkers ↑, troponins ↑

Warning signs for disease progression

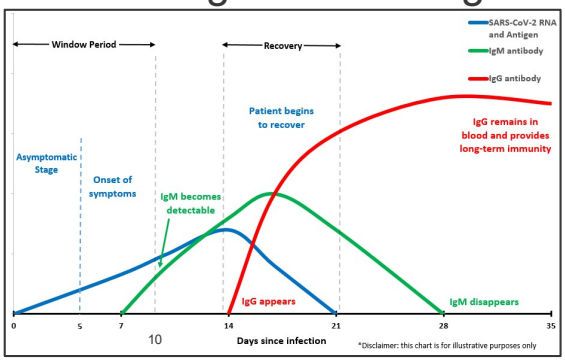
1) Lymphocytes ↓↓↓
2) Inflammatory markers ↑↑↑ (CRP, IL-6)
3) Lactic acid ↑↑↑
4) Pulmonary lesion on chest imaging ↑↑↑

COVID-19: Lab-etiological & serological Examination

	Etiological examination	Serological examination
Target	Viral nucleic acid	Specific IgM/IgG antibody against virus
Mechanism	RT-PCR & NGS	GICA, ELISA, CLIA
Specimen	Upper airway (nasopharyngeal swab specimen) Lower airway (**sputum**)	Serum
Suggestion	Continual test if negative at the beginning	Suspected cases with negative nucleic acid

RT-PCR, real-time polymerase chain reaction

COVID-19: Lab-etiological & serological Examination



Viral nucleic acid test

Test results			Clinical Significance
PCR	IgM	IgG	
+	–	–	Patient may be in the window period of infection.
+	+	–	Patient may be in the early stage of infection.
+	+	+	Patient is in the active phase of infection.
+	–	+	Patient may be in the late or recurrent stage of infection.
–	+	–	Patient may be in the early stage of infection. PCR result may be false-negative.
–	–	+	Patient may have had a past infection, and has recovered.
–	+	+	Patient may be in the recovery stage of an infection, or the PCR result may be false-negative.

PCR, polymerase chain reaction

https://www.biopanda.co.uk/

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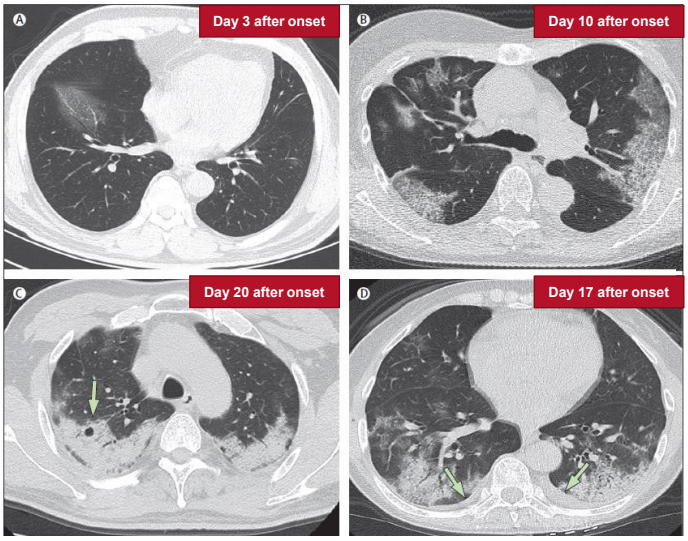
COVID-19: Chest CT Imaging



- (A) 56 y/o man: focal ground-glass opacity associated with smooth interlobular and intralobular septal thickening in the right lower lobes
- (B) 74 y/o woman: bilateral, peripheral ground-glass opacity associated with smooth interlobular and intralobular septal thickening (crazy-paving pattern).
- (C) 61 y/o woman: bilateral and peripheral predominant consolidation pattern with a round cystic change internally (arrow)
- (D) 63 y/o woman: bilateral, peripheral mixed pattern associated with air bronchograms in both lower and upper lobes, with a small amount of pleural effusion (arrows)

Shi H, et al. Lancet Infect Dis. 2020 Feb 24.

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COVID-19: Chest CT & Viral Nucleic Acid

- Based on positive RT-PCR, chest CT sensitivity: 97%
- Based on positive RT-PCR, chest CT specificity: 25%
- 60%~93% pts. had initial positive CT consistent with COVID-19 prior (or parallel) to the initial positive RT-PCR

Ai T, et al. Radiology. 2020 Feb 26:200642.

- Chest CT abnormalities identified in patients prior to the development of symptoms

Shi H, et al. Lancet Infect Dis. 2020 Feb 24.

CT imaging is very useful for COVID-19 clinical diagnosis, esp. in epidemic area (high sensitivity, easy access & rapid knowing results)

Classic CT imaging & symptom, even negative RT-PCR: Isolation and continuous RT-PCRs

RT-PCR, real-time polymerase chain reaction

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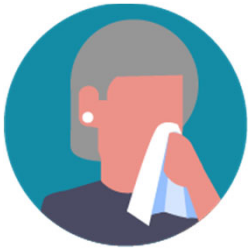
COVID-19: Basic Protective Measures


Cover your mouth and nose with a cloth face cover when around others

Stay home as much as possible

CDC (US): How to Protect Yourself & Others, updated April 4, 2020

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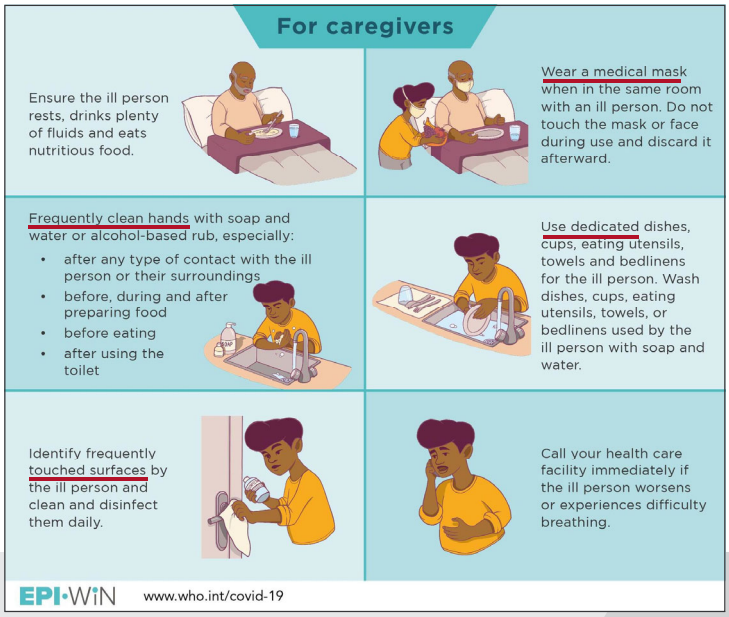
COVID-19: Protections When Caring for Suspected/Confirmed Cases



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COVID-19: Other Protective Measures in China

Temperature check

Disinfection in public places

Fangcang Hosp.

Prevention propagation

Wearing mask in public places

Quarantine doesn't separate us from love and care

Mutual help based on community

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COVID-19: Personal Protection Equipment (health worker)

Protection Level	Protective Equipment	Scope of Application
Level I protection	• Disposable surgical cap • Disposable surgical mask • Work uniform • Disposable latex gloves or/and disposable isolation clothing if necessary	• Pre-examination triage, general outpatient department
Level II protection	• Disposable surgical cap • Medical protective mask (N95) • Work uniform • Disposable medical protective uniform • Disposable latex gloves • Goggles	• Fever outpatient department • Isolation ward area (including isolated intensive ICU) • Non-respiratory specimen examination of suspected/confirmed patients • Imaging examination of suspected/confirmed patients • Cleaning of surgical instruments used with suspected/confirmed patients
Level III protection	• Disposable surgical cap • Medical protective mask (N95) • Work uniform • Disposable medical protective uniform • Disposable latex gloves • Full-face respiratory protective devices or powered air-purifying respirator	• When the staff performs operations such as tracheal intubation, tracheotomy, bronchofibroscope, gastroenterological endoscope, etc., during which, the suspected/confirmed patients may spray or splash respiratory secretions or body fluids/blood • When the staff performs surgery and autopsy for confirmed/suspected patients • When the staff carries out NAT for COVID-19

- **Surgical mask**

  All staff at the healthcare facilities

- **N95 mask based on Level I protection**

  Staff in Emergency dept., outpatient dept. of infectious disease, outpatient dept. of respiratory care, stomatology/endoscopic room

- **Protective face screen based on Level II protection**

  Staff collecting respiratory specimens

Tingbo Liang, et al. Handbook of COVID-19 Prevention and Treatment

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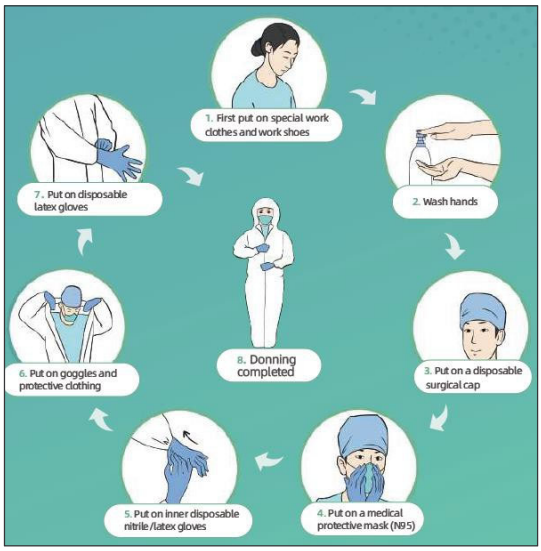
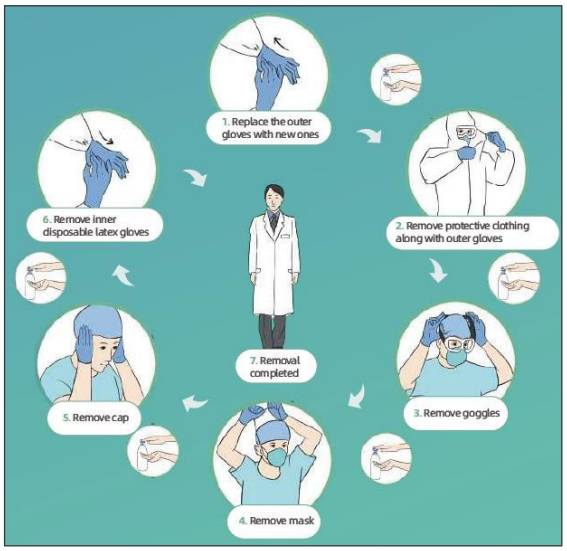
COVID-19: Personal Protection Equipment (health worker)





Tingbo Liang, et al. Handbook of COVID-19 Prevention and Treatment

COVID-19: Self-evaluation

- **Indications for home care**

  T<38℃, mild symptom, no obvious SoB or dyspnea

  No travel to epidemic area, no contact people from epidemic area, no clustering onset within 14 days before illness

  No chronic respiratory, cardiovascular disease…

  Not pregnant women, children, or the elderly

- **Indications for seeking medical advice** (one of following criteria)

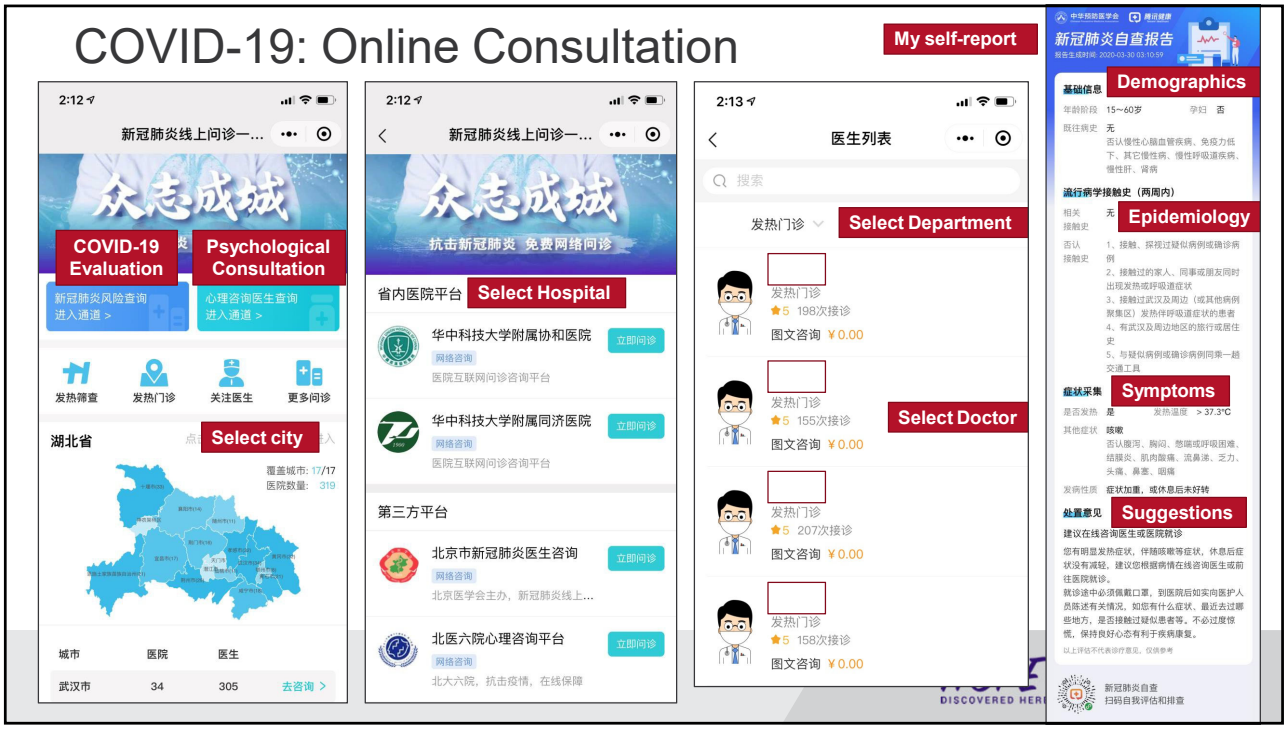
  T≥38℃, no symptom improvement or deterioration after 1~2 days home care

  Travel to epidemic area or contact people from epidemic area recently

  Close contact with symptomatic patients

  The elderly, pregnant women, children, patients w/ chronic diseases (lung, heart, liver, kindey) or immunocompromise

→ **Online Consultation or Fever Clinic**



COVID-19: Screen Criteria in Clinical Settings

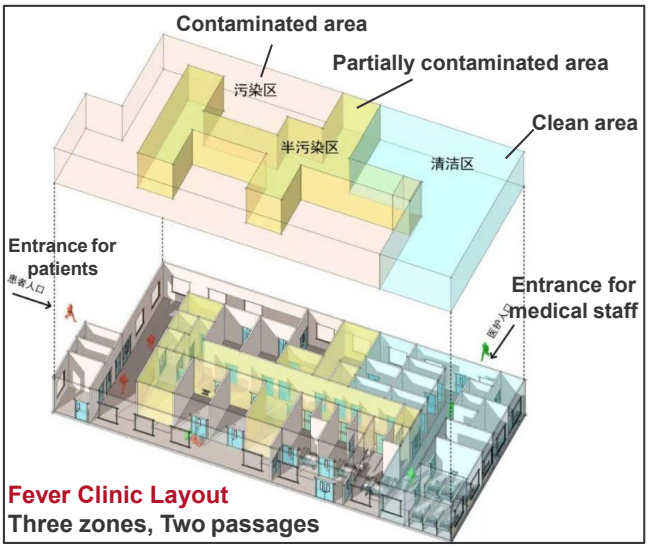
- **Epidemiological history**
  - Travel or residence in epidemic area within 14 days before illness
  - Contact with COVID-19-infected persons within 14 days before illness
  - Contract with patients presenting symptoms, who travel to epidemic area within 14 days before illness
  - Clustering onset (≥ 2 symptomatic cases within 2 weeks in small area)
- **Clinical manifestation**
  - Fever and/or respiratory symptoms
  - Imaging features of COVID-19 pneumonia
  - Total leukocytes -/↓, lymphocyte -/↓ (early stage)

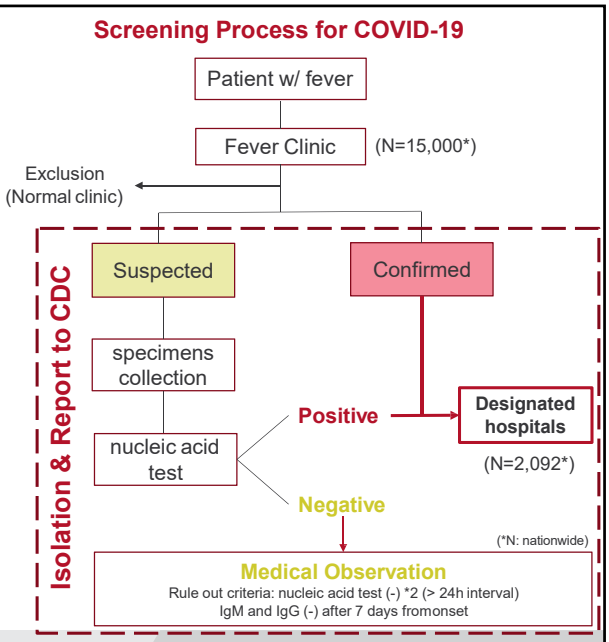
Suspected Case
1 epidemiological criterion + 2 clinical criteria
OR 3 clinical criteria

Real-time RT-PCR for COVID-19 nucleic acid: positive
Gene sequencing: highly homologous with COVID-19
COVID-19 specific IgM and IgG: positive

Confirmed Case

COVID-19: Fever Clinic





COVID-19: Fangcang Shelter hospital

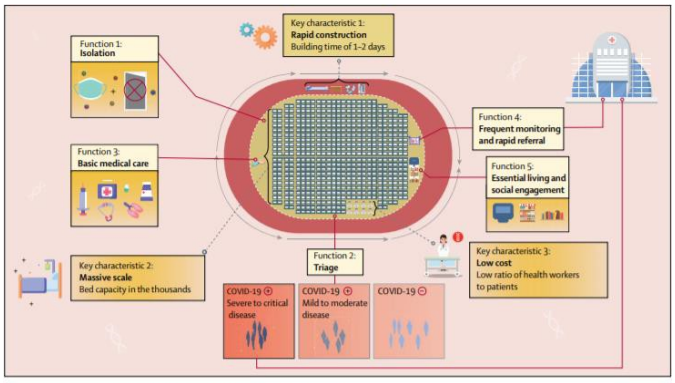


Figure 3: Key characteristics and essential functions of Fangcang shelter hospitals

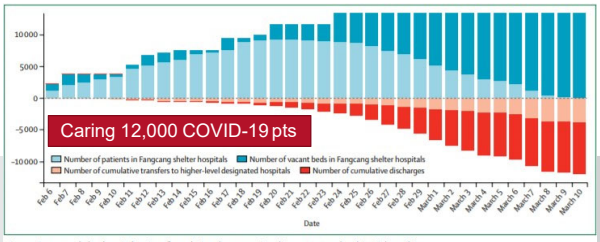


Figure 1: Fangcang shelter hospital patient flows during the coronavirus disease 2019 outbreak in Wuhan, China

Simiao Chen, et al. Lancet, April 2, 2020

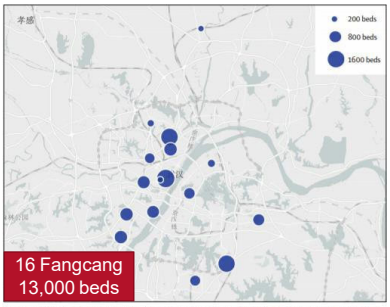
COVID-19: Fangcang Shelter hospital

Admission Criteria	Reason for criterion	Alternative care pathway if criterion is not met
Positive COVID-19 test with mild signs or symptoms (mild clinical symptoms, imaging shows no signs of pneumonia) to moderate signs or symptoms (fever, respiratory tract symptoms, imaging shows pneumonia)	The primary purpose of the Fangcang shelter hospitals is to greatly expand capacity to care for COVID-19 patients with mild to moderate signs or symptoms	Patients with severe signs or symptoms are referred to higher-level hospitals; suspected cases are referred to quarantine locations with continued community screening for COVID-19
Ability to walk and live independently	Fangcang shelter hospitals cannot provide intensive care for patients who cannot take care of themselves	Referred to higher-level hospitals
Absence of severe chronic diseases, including hypertension, diabetes, coronary heart disease, malignancy, structural lung disease, pulmonary heart disease, and immunosuppression	Early evidence suggests that patients with underlying health conditions, such as hypertension, diabetes, and cardiovascular disease, are more likely than patients without these comorbidities to develop severe COVID-19[35,40,63]	Referred to higher-level hospitals
No history of mental health conditions	Fangcang shelter hospitals do not have the capacity to treat psychiatric diseases; in addition, early evidence suggests that patients with some mental health conditions, such as anorexia nervosa, are more likely to develop severe COVID-19[40]	Referred to higher-level hospitals
<65 years old	Early evidence suggests that older patients are at considerably increased risk of developing severe COVID-19[35,40,63]	Referred to higher-level hospitals
Negative influenza test	Admission to Fangcang shelter hospitals should not increase the risk of influenza co-infection[62]	Referred to higher-level hospitals
SpO2 >93% and breathing rate <30 beats per min in resting state	Oxygen saturation and breathing rate are important physiological parameters of the respiratory and circulatory system, and are used to gauge the severity of COVID-19;[43,44] early evidence suggests that patients with dyspnoea and hypoxia (SpO2 <93%) should receive supplemental oxygen and be admitted to an isolation ward[45]	Referred to higher-level hospitals

These criteria were applied during the COVID-19 outbreak in Wuhan, China in February to March, 2020.[5,62] COVID-19=coronavirus disease 2019. SpO2=blood oxygen saturation.

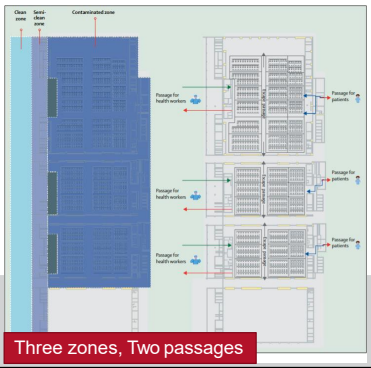
Table: **Fangcang shelter hospital admission criteria**

Simiao Chen, et al. Lancet, April 2, 2020



16 Fangcang
13,000 beds

Figure 4: Fangcang shelter hospital locations and capacities during the coronavirus disease 2019 outbreak in Wuhan, China



Three zones, Two passages

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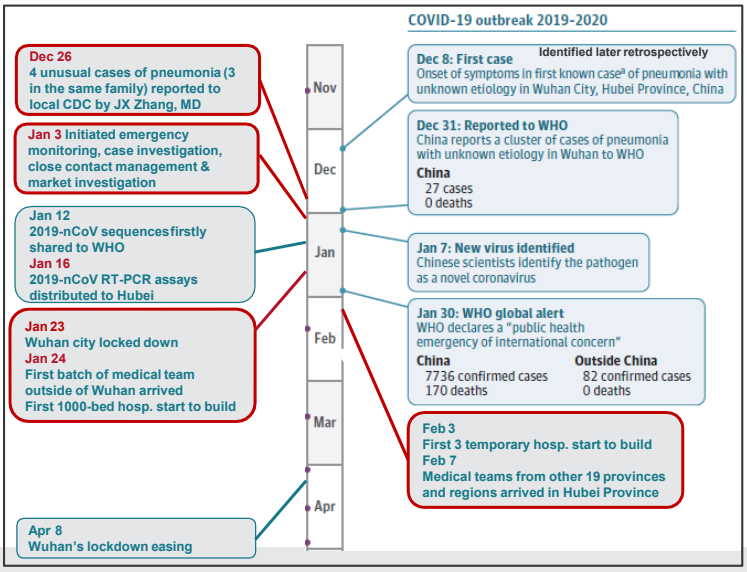
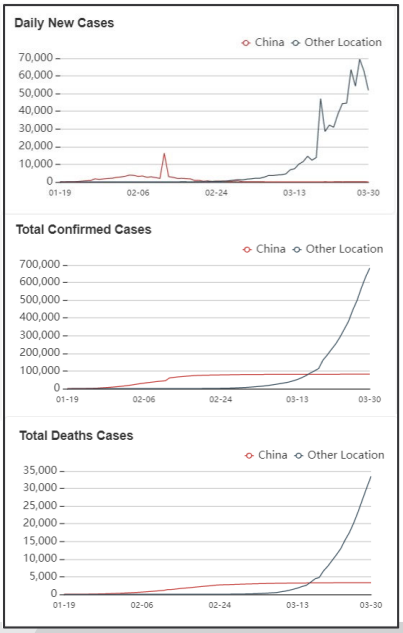
Creating a world without heart and vascular disease

Wuhan, China (武汉 [武漢]，中国)

From Wikipedia-Wuhan

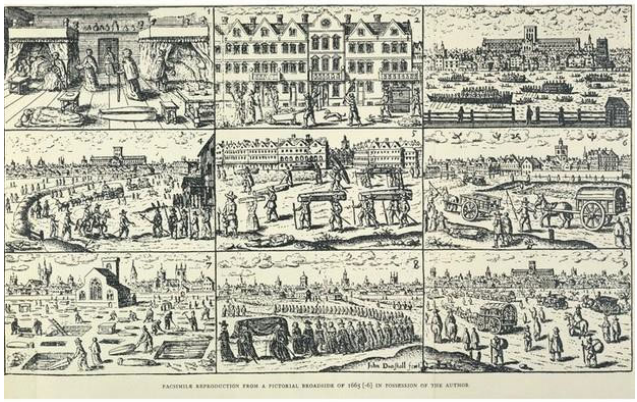
China's Efforts on COVID-19 Pandemic



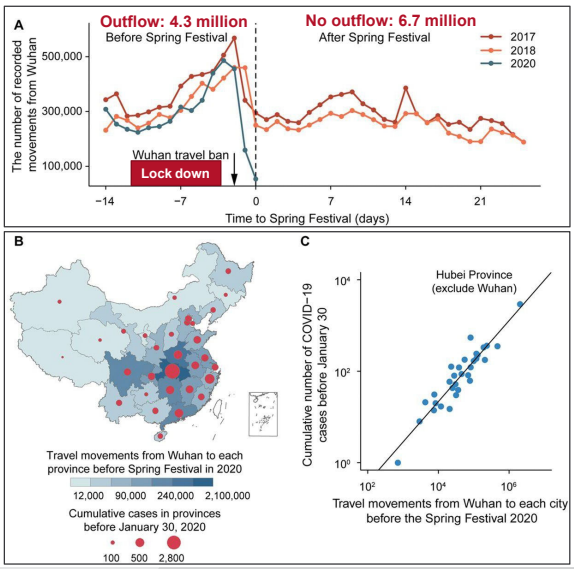


Wu Z, et al. JAMA. 2020 Feb 24. Report of the WHO-China Joint Mission on COVID-19

Action Against COVID-19: Lock Down & Shut Down



The Black Death Quarantine



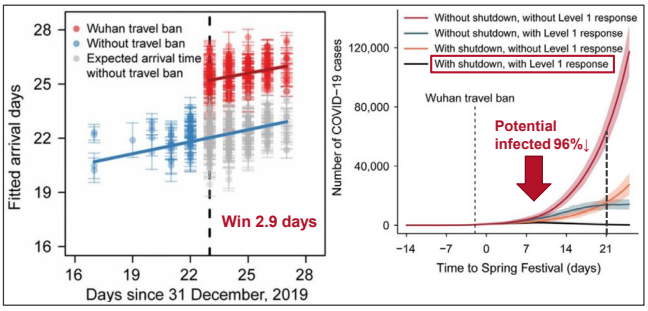
Huaiyu Tian, et al. Science 31 Mar 2020: eabb6105

Action Against COVID-19: Lock Down & Shut Down

Level 1 response to major public health emergencies	Number of cities implementing control measures	Average lags (days) between implementation and 31 December 2019‡
Identify the affected area of a city*	342	0
Close schools*	342	0
Close entertainment venues and ban public gatherings	220	27.17 (2.82)
Isolate patients with infectious diseases*	342	0
Isolate suspected patients*	342	0
Suspend intra-city public transport (bus and subway)	136	29.00 (2.60)
Prohibit inter-city travel	219	27.86 (1.49)
Collect, evaluate, report and publish information on public health emergencies daily*	342	0
Assist subdistrict, township (town), neighbourhood and village committee staff*	342	25.32 (1.07)

Shut down

342 cities



Travel ban & national emergency response **delayed** the growth and **limited** the size of the COVID-19 epidemic

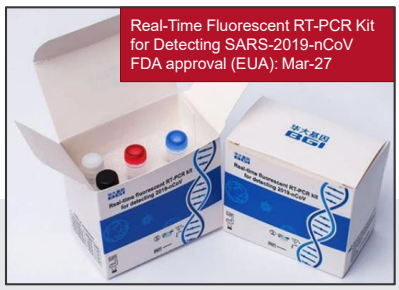
Huaiyu Tian, et al. Science 31 Mar 2020: eabb6105

Action Against COVID-19: Intensive Testing

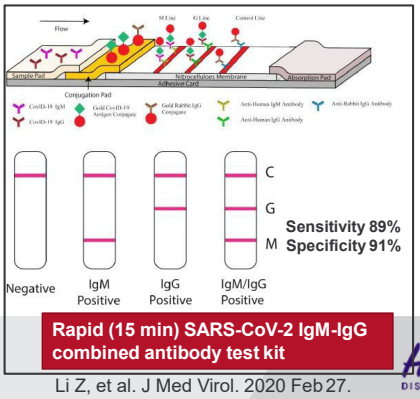
210,000 tests nationwide, 56,000 in Wuhan

Respiratory Virus Nucleic Acid Detection Kit (Isothermal Amplification Chip Method
CE-IVD approval: Mar-26

Detecting 6 respiratory viruses (including SARS-CoV-2) within 1.5 hrs



Real-Time Fluorescent RT-PCR Kit for Detecting SARS-2019-nCoV
FDA approval (EUA): Mar-27



Rapid (15 min) SARS-CoV-2 IgM-IgG combined antibody test kit

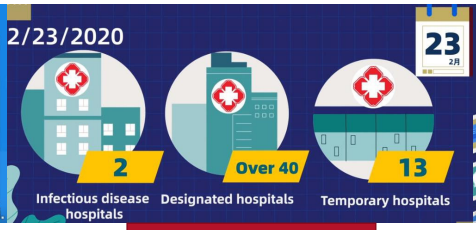
Li Z, et al. J Med Virol. 2020 Feb 27.

Artificial intelligence assisted COVID-19 imaging diagnosis

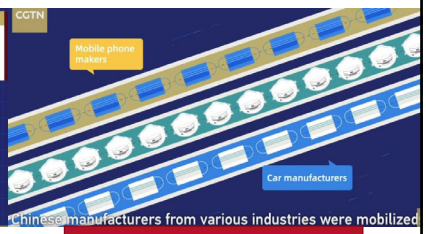
20s per scan, accuracy 96%

Action Against COVID-19: Medical Backup & Free for Treatment

330 medical teams, 416,000 medics



> 40,000 hospitals beds
> 70,000 quarantine beds



Daily mask production
8 to 55.4 million within 1 month

Medical team from Beijing Anzhen Hospital
11 health workers, 65 days in Wuhan

Liang Tang, MD
MHI scholar (17~19)
Xiangya Hospital 52 days in Wuhan

Action Against COVID-19: International Support

From 71 counties & 9 international organizations

WHO-China Joint Mission

Dr. Lipkin & Dr. Zhong sharing opinions on COVID-19

Overseas Chinese people & students donate PPE to the frontline in Wuhan

COVID-19: Second Wave in China?

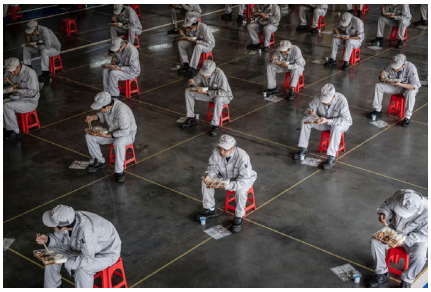
- Containment measures easing gradually with ultra-caution in China

  Close monitoring, extensive testing & contract tracing to new cases

  Maintaining social-distancing practices (some factories reopened, schools closed)

  Closing borders (returning residents quarantined for 14 days)

  Vaccines undergoing research and development



Staff at a car-manufacturing plant in Wuhan, social-distancing measures during lunch break

Barcode containing health details & travel history
Red: confirmed cases (To Yellow: discharge+14 days quarantine; To Green: another 14 days quarantine at home)
Yellow: suspected cases or turning from Red (To Green: RT-PCR negative+14 days quarantine)
Green: remain in safe area, turning from Red/Yellow→return to work, use public transportations & cross provincial borders

https://www.nature.com/articles/d41586-020-00938-0

Outline

- What is the COVID-19?
- How to prevent & identify COVID-19 infection?
- How to control COVID-19 pandemic?
- How to manage patients with COVID-19?
- COVID-19 & Cardiovascular Disease

COVID-19: General Treatment

- **Rest in bed with supportive treatment**

  Sufficient energy supply, water and electrolyte balance

- **Monitor**

  Vital signs, O_2%

  Blood/urine routine, CRP, biochemical indicators, coagulation, ABG, chest imaging, cytokine

- **O_2 therapy**

  Nasal cannula, mask O_2, high-flow nasal cannula O_2 therapy

COVID-19: Antiviral Therapy **Empirical Treatment**

Medication	Dosage and usage (for adult)
α-interferon	5 million U + 2ml sterile water, 2 times/day, inhalation (in negative pressure ward)
Lopinavir/Ritonavir	200 mg/50 mg/capsule, 2 capsules each time, 2 times/day, treatment course≤10 days
Ribavirin	500 mg each time, 2~3 times/day, intravenous infusions, treatment course≤10 days, **Recommend Ribavirin combination with Interferon or Lopinavir/Ritonavir**
Chloroquine phosphate	Weight>50kg: 500 mg each time, 2 times/day for 7 days Weight<50kg: 500 mg each time, 2 times/day for day 1 and day2; 1 time/day for day 3-7 **Contraindication: heart disease**
Abidol	200 mg each time, 3 times/day, treatment course≤10 days

- **Attention:**

  Adverse reactions, contraindications, interactions with other drugs, fetal toxicity

  No recommendation for ≥ 3 antivirus drugs at the same time

  Avoid inappropriate use of antibacterial drugs

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COVID-19: Developing Vaccines

Vaccine Platforms, Their Attributes, and the Status of Vaccine Candidates.*

Technology	Attributes				Candidates in Preclinical Development	Candidates in Phase 1
	Single Dose	Licensed Platform	Speed	Current Scale		
DNA	No	No	Fast	Medium	Inovio Pharmaceuticals Takis/Applied DNA Sciences/Evvivax Zydus Cadila	
Inactivated	No	Yes	Medium	Medium to high	Sinovac	
Live attenuated	Yes	Yes	Slow	High	Codagenix/Serum Institute of India	
Nonreplicating vector	Yes	No	Medium	High	GeoVax/BravoVax Janssen Pharmaceutical Companies University of Oxford Altimmune Greffex Vaxart ExpreS2ion	CanSino Biologics (ChiCTR20000 30906)
Protein subunit	No	Yes	Medium to fast	High	WRAIR/U.S. Army Medical Research Institute of Infectious Diseases Clover Biopharmaceuticals Inc/GSK Vaxil Bio Aj Vaccines Genrex/EpiVax/University of Georgia Sanofi Pasteur Novavax Heat Biologics/University of Miami University of Queensland/GSK/ Baylor College of Medicine iBio/CC-Pharming	
Replicating viral vector	Yes	Yes	Medium	High	Zydus Cadila Institut Pasteur/Themis Tonix Pharma/Southern Research	
RNA	No	No	Fast	Low to medium	Fudan University/Shanghai JiaoTong University/RNACure Biopharma China CDC/Tongji University/Stermina Arcturus/Duke-NUS Imperial College London Curevac BioNTech/Pfizer	Moderna/NIAID (NCT04283461)
Uncertain					University of Pittsburgh University of Saskatchewan ImmunoPrecise MIGAL Galilee Research Institute Doherty Institute Tulane University	

Nicole, et al. NEJM, March 30, 2020

* Attributes refer to general attributes of the platform, and assessments are not intended as inferences about a particular candidate. NIAID denotes National Institute of Allergy and Infectious Diseases, and WRAIR Walter Reed Army Institute of Research.

A single-center, open and dose-escalation phase I clinical trial for recombinant novel coronavirus vaccine (adenoviral vector) in healthy adults aged between 18 and 60 years

Low-dose Group (N=36) · Middle-dose Group (N=36) · High-dose Group (N=36)

ChiCTR2000030906

Adverse reactions 7 days post injection (Primary indicator)
Adverse reactions 28 days post injection
SAE 6 months post injection
Anti-S antibody IgG Day 14, 28, month 3 and 6 post injection
Neutralizing antibody against SARS-CoV-2 Day 14, 28, month 3 post injection
Eutralizing antibody against Ad5 Day 14, 28, month 3 and 6 post injection
Specific T cell response Day 14, 28 and month 6 post injection
Changes of the laboratory safety examinations Day 0, day 7

By April 2, all eligible volunteers got vaccine injection
18 volunteers finished isolation with good conditions

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COVID-19: Traditional Chinese Medicine Treatment

- **Utilization** (w/ or w/o western medicine) **> 90% in confirmed cases**
- **Mild type/recovery phase**：w/ or w/o western medicine → relief symptom, reduce progression to severe type
- **Severe type**：Inhibition of cytokine storm

Three Drugs, Three Prescriptions

- 清肺排毒汤由麻黄、炙甘草、杏仁、生石膏、桂枝、泽泻、猪苓、白术、茯苓、柴胡、黄芩、姜半夏、生姜、紫菀、冬花、射干、细辛、山药、枳实、陈皮、藿香等组成。
- 化湿败毒方由生麻黄、杏仁、生石膏、甘草、藿香、厚朴、苍术、草果、法半夏、茯苓、生大黄、生黄芪、葶苈子、赤芍等组成。
- 宣肺败毒汤由麻黄、杏仁、石膏、甘草、虎杖、马鞭草、苇茎、薏苡仁、冬瓜子、桃仁、葶苈、薏苡仁等组成。

COVID-19: Treatment of Severe & Critically Severe Cases

- **Principles**

  Treatment: symptom, underlying diseases

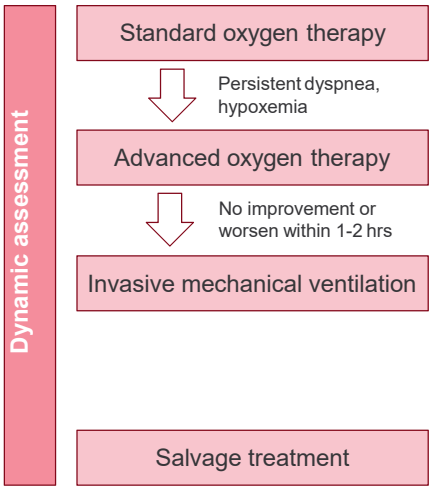
  Prevention: complications, secondary infections

  Support: multiple organ function

- **Management** **Multidisciplinary Collaboration & Management**

Respiratory support	**Recovered patients' plasma therapy**
Circulatory support	**Blood purification treatment**
Renal failure and renal replacement therapy	**Immunotherapy**

Severe & Critically Severe COVID-19: Respiratory Support



Nasal cannula, mask O_2

Hydrogen/oxygen mixed gas (66.6%/33.3%) inhalation might improve dyspnea

High-flow nasal cannula O_2, non-invasive mechanical ventilation

Lung protective ventilation: small tidal volume, low plateau pressure

High PEEP: when airway plateau pressure≤35 cm H_2O

Keep airway warm, humid, avoid prolonged sedation, early pulmonary rehabilitation

Closed sputum suction, bronchoscopy if necessary

Lung expansion: severe adult respiratory distress syndrome (ARDS)
Prone position ventilation: >12 hrs/d
ECMO: prone ventilation is not effective
Indications: FiO_2>90%, oxygenation index<80mmHg, lasting>3~4 hrs;
Mode: VV mode: simple respiratory failure, plateau pressure≥35 cm H_2O;
VA mode: circulatory support needed
Weaning trails: underlying disease controlled, cardiopulmonary function began to recover

Positive pressure ventilation might induce viral aerosol formation!

Severe & Critically Severe COVID-19: Circulatory Support

- **Consider to use**

  Adequate fluid resuscitation, microcirculation improvement and vasoactive agents

- **Close monitor**

  BP, HR, urine output, ABG (lactic acid, base excess)

  Fluid balance

  Noninvasive/invasive hemodynamic monitoring (Doppler echo, echo, invasive BP, PiCCO)

- **Attention: septic shock, GI bleeding, severe heart failure**

PiCCO, pulse-indicated continuous cardiac output

Severe & Critically Severe COVID-19: Renal Failure Treatment

- **Etiological treatment** (eg. hypoperfusion, drugs)
- **Monitoring**

  Fluid balance, acid-base balance and electrolyte balance

  Nitrogen balance, calorie and minerals supplement
- **Renal replacement therapy (CRRT)**

  Indications: ① hyperkalemia; ② acidosis; ③ pulmonary edema or excessive water load;

  ④ fluid management when multiple organ dysfunction occurs

Severe & Critically Severe COVID-19: Recovered Patients' Plasma Therapy

- **Indication:** severe or critically severe patients with rapid disease progression
- **Contraindication**

  Allergy history of plasma, sodium citrate and methylene blue

  Autoimmune system diseases or selective IgA deficiency
- **Infusion dosage:** ≥ 400 ml/fusion, or ≥ 200 ml/fusion * multiple times
- **Donor**

  Age 18~55 y/o, weight > 50kg (male)/45kg (female)

  ≥ 3 weeks from onset of symptoms

  Meeting discharge criteria

  No history of blood transmitted diseases

  Lab test for SARS-CoV-2 negative

  Nucleic acid test, 160-/320-fold dilution for qualitative test of virus-specific IgG & IgM, viral neutralization test

Severe & Critically Severe COVID-19: Blood Purification Treatment

- **Component**

  Plasma exchange, absorption, perfusion, blood/plasma filtration…

- **Objective**

  Remove inflammatory factors, reduce the "**Cytokine Storm**"

- **Indication**

  Early and mid-term cytokine storm

Severe & Critically Severe COVID-19: Immunotherapy

- **Indication**

  Extensive lung lesion, elevated Interleuki-6 levels

- **Tocilizumab**

  First dose 4-8 mg/kg, recommended dose 400 mg + 0.9% saline to 100 ml, infusion time > 1 hr

  If first medication ineffective, try second time after 12 hrs (same dose)

  Cumulative administrations ≤ 2 times, max. single dose ≤ 800 mg

  Attention to allergic reactions, not recommended for active infections

Severe & Critically Severe COVID-19: Other Treatments

- **Glucocorticoids** **WHO not recommend, unless COPD/asthma exacerbation**

  Indication: progressive deterioration (oxygenation, imaging, inflammatory response)

  Short-term (3~5 days) use, Dosage: methylprednisolone ≤ 1~2 mg/kg/day

  Large doses is not recommended: delay removal of coronavirus

- **Intestinal micro-ecological regulator**

  Maintain intestinal micro-ecological balance, prevent secondary bacterial infections

- **Intravenous gamma globulin**
- **Pregnant women:** pregnancy termination or cesarean delivery (preferred)
- **Psychological counseling:** anxiety, fear

COVID-19: Discharge Criteria & Precautions

- **Discharge Criteria** (meet all of below conditions)

  Body temperature: normal for > 3 days

  Respiratory symptoms: significant improvement

  Pulmonary imaging: marked improvement

  Nucleic acid test: negative for two consecutive times (> 24 hrs interval)

- **Precautions after discharge**

  Share medical records to basic medical and health institutions

  Recommend isolation and health monitoring for 14 days

  Follow up in the 2nd and 4th week after discharge

Outline

- What is the coronavirus disease 2019 (COVID-19)?
- How to prevent & identify COVID-19 infection?
- How to control COVID-19 pandemic?
- How to manage patients with COVID-19?
- COVID-19 & Cardiovascular Disease

COVID-19 & Cardiovascular Disease

- **Common comorbidities**

  HTN (14~22%), DM (6~11%), CVD (4~7%), respiratory disease (1~3%)

  Yang J, et al. Int J Infect Dis. 2020 Mar 12.

- **Acute cardiac injury**

  Common in severe cases, even in patients without pre-existing CVD

  Presenting cardiac symptoms & seeing a cardiologist, then diagnosis

- **Patients with pre-existing CVD**

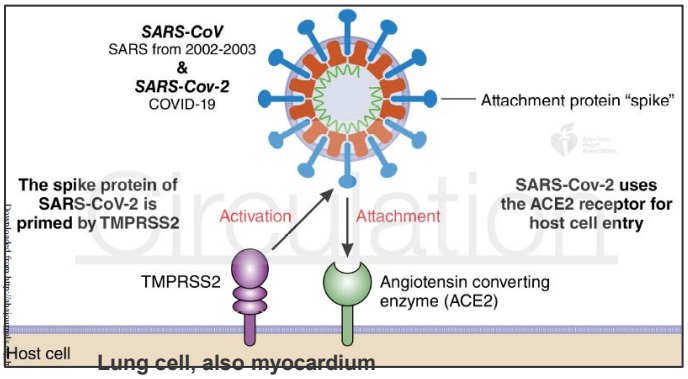
  More likely to be infected, developed severe symptoms, even had high mortality

- **Patients taking antiviral drugs**

  Drug-related heart damage should not be ignored

  Zheng et al. Nat Rev Cardiol. 2020 Mar 5.

COVID-19 & Myocardial Injury: Potential Mechanism



- Virus invades myocardium, leading to myocardial injuries and myocarditis
- Cytokine storm
  - Pro-inflammatory factors ↑↑ (dose-effect)
  - Anti-inflammatory factors ↑ (feedback & adjustment)
- Pulmonary infectious
  - Hypoxemia/hypotension, imbalance of myocardial O_2 supply

Clerkin et al. Circulation. 2020 Mar 21.

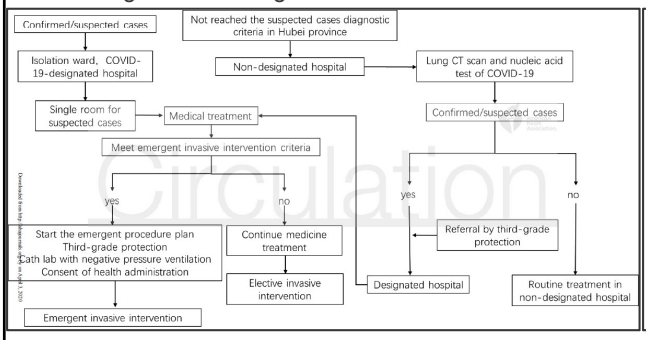
- Withdrawal of ACEi or ARB in COVID-19 patients? No, robust evidence is lacking!

Clerkin et al. European Heart Journal (2020) 0, 1–3

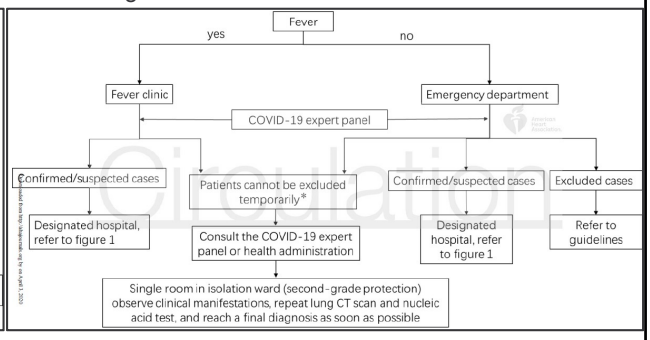
COVID-19: Critical Cardiovascular Disease Management

Chinese Society of Cardiology Expert Consensus on Managing CVD during COVID-19 Epidemic

Regions with a high incidence of COVID-19



Regions with a low incidence of COVID-19



COVID-19: Critical Cardiovascular Disease Management

Chinese Society of Cardiology Expert Consensus on Managing CVD during COVID-19 Epidemic

Table 1. Patients with severe emergent cardiovascular diseases for whom hospitalization and conservative medical treatment is recommended during COVID-19 epidemic.

Patients with severe emergent cardiovascular diseases
1. Patients with STEMI for whom thrombolytic therapy is indicated*.
2. STEMI patients presenting after exceeding the optimal window of time for revascularization but yet with worsen symptoms, such as severe chest pain, continuous ST-segment elevation, or myocardial infarction-related mechanical complications.
3. High risk NSTE-ACS patients (GRACE score ≥ 140).
4. Patients with uncomplicated Stanford type B aortic dissection#.
5. Patients with acute pulmonary embolism.
6. Patients with acute exacerbation of heart failure.
7. Patients with hypertensive emergency.

STEMI, ST-segment elevation myocardial infarction; NSTE-ACS, non-ST elevation acute coronary syndromes; GRACE, Global Registry of Acute Coronary Events.
*The third- generation thrombolytic agents are preferred.
#For Stanford type A aortic dissection, surgical treatment is recommended.

Table 2. Severe cardiovascular diseases requiring urgent or emergent intervention or surgery.

Patients with severe cardiovascular diseases
1. Acute STEMI with hemodynamic instability.
2. Life-threatening NSTEMI indicated for urgent revascularization.
3. Stanford type A or complex Type B acute aortic dissection.
4. Bradyarrhythmia complicated with syncope or unstable hemodynamics mandating implantation of a temporary (bedside implantation as far as possible), or, if indicated, permanent pacemaker.
5. Pulmonary embolism presenting with hemodynamic instability for whom regular intravenous thrombolytic therapy might lead to excessively risk of intracranial bleeding, and trans-catheter low-dose thrombolysis in the pulmonary artery may be required.

STEMI, ST-segment elevation myocardial infarction; NSTEMI, Non-ST segment elevation myocardial infarction.

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COVID-19: Unanswered Questions

Panel 1. Key unanswered questions of the Covid-19 outbreak
➔ Epidemiology
** What is the optimal strategy for identifying contacts of infected individuals?
** To which extent has the virus mutated during the global transmission?
** What is the proportion of super-spreaders among the whole cohort of patients with Covid-19?
➔ Virology and Clinical courses
** Is there evidence of pre-symptomatic viral shedding?
** What is the time point of viral shedding and what is the association with disease progression?
** Are patients with a relapse of positive viral RNA findings contagious when discharged home? ** What is the natural course of severe and non-severe cases? ➔ Pathogenesis and prognosis ** What is the characteristic and mechanism of mucus hypersecretion in small airways? ** How does SARS-CoV-2 result in lymphopenia and inflammatory cytokine storm? ** What is the most valuable biomarker for predicting the clinical outcomes of Covid-19? ** Could artificial intelligence aid in the diagnosis and phenotyping Covid-19? ➔ Treatment ** Will inhibitors of viral replication be effective in the clearance of Covid-19? ** What are the most cost-effective managements for Covid-19? ** When should be the optimal timing and duration for intubation? ** Which medication(s) may be useful to suppress the inflammatory cytokine storm?

Wei-jie Guan et al. European Respiratory Journal 2020

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COVID-19: Free Online Resources

- Chinese Clinical Guidance for COVID-19 Pneumonia Diagnosis and Treatment (7th edition)

  published by China National Health Commission on March 4, 2020

  http://kjfy.meetingchina.org/msite/news/show/cn/3337.html

- Guidance for Corona Virus Disease 2019: Prevention, Control, Diagnosis and Management

  published by China National Health Commission

  https://mp.weixin.qq.com/s/bwlkBTJLe2oORWRUs1N5yQ

- Report of the WHO-China Joint Mission on Coronavirus Disease 2019 (COVID-19)

  published by WHO-China Joint Mission

  https://www.who.int/docs/default-source/coronaviruse/who-china-joint-mission-on-covid-19-final-report.pdf

- Handbook of COVID-19 Prevention and Treatment

  published by Jack Ma Foundation, Alibaba Foundation, The First Affiliated Hospital, Zhejiang University School of Medicine

  https://www.alibabacloud.com/zh/universal-service/pdf_reader?pdf=Handbook_of_COVID_19_Prevention_en_Mobile.pdf

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Questions & Answers

Thanks for your attention

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