COVID-19 clinical treatment and research experiences from Shanghai, China

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Globally, 292,142 confirmed and 12,784 deaths reported as to March 22, 2020.

**Distribution of COVID-19 cases as of 21 March 2020, 23:59 (CET)**

- **Confirmed** cases reported between 13 and 19 February 2020 include both laboratory-confirmed and clinically diagnosed (only applicable to Hubei province); for all other dates, only laboratory-confirmed cases are shown.

- 712 cases are identified on a cruise ship currently in Japanese territorial waters.

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**Number of Confirmed cases**

- 1 - 10
- 11 - 100
- 101 - 1000
- 1001 - 5000
- 5001 - 10,000
- 10,001 - 30,000
- > 30,000

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*Country, area or territory with cases*

The boundaries and names shown and the designations used on this map do not imply the expression of any opinion whatsoever on the part of the World Health Organization concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. Dashed and dashed lines on maps represent approximate border lines for which there may not yet be full agreement.
How to stop the virus circulation in a metropolis: The epidemic trend in Shanghai and the disease prevention/control measures
The epidemic trend in Shanghai

- Top-level response to the major public health emergency
- Lockdown of Wuhan
- Resumption of Work
- Foreign imported cases

Sources: HZ Lu, JW Ai, WH Zhanget al. medRxiv
2020.02.19.20025031; doi:https://doi.org/10.1101/2020.02.19.2002503
The epidemics trend of Shanghai (actual vs. predicted)

- The previous epidemics trend prediction of Shanghai by several studies if the transmission was not stopped.
- Shanghai has indeed managed to stopped the exponential growth in less than 2 weeks.

Sources: HZ Lu, JW Ai, WH Zhanget al. medRxiv
2020.02.19.20025031; doi:https://doi.org/10.1101/2020.02.19.2002503
Multiple measures in Shanghai government in the early stage of the epidemics

**Lock Down:** The population travelling to or leaving Shanghai has significantly decreased by approximately 50%.

**Slow Down:** All gathering activities and most of the recreational sites including restaurants, theatres and etc. were closed.

**Stay at Home:** Shanghai extended the Spring Festival holidays to 17 days from Jan 24th until Feb 9th to minimize the possible infections from patients in their incubation period. All citizens were encouraged to stay at home unless for necessary working, shopping, or medical treatment.
Find every patient among suspected cases

2. Optimizing diagnostic flow chart for COVID-19 diagnosis
Criteria to request a SARS-CoV-2 test

● Shanghai opened 117 designated fever clinics. **Now plus more 182 fever sentinel hospital**

● **ALL patients** who met **1 epidemiology criteria+1 clinical relevant symptoms** can go to these clinics.

● Suspected COVID-19 patients would be admitted into the quarantine ward and CDC staff would come for sampling and epidemiological question.

● If nucleic acid test turned our positive, **all patients were enrolled into the designated hospital in Shanghai**
## More than SARS-CoV-2 RT-PCR in Huashan Hospital Shanghai

<table>
<thead>
<tr>
<th>Diagnostic methods</th>
<th>Laboratory-confirmed cases (n=20)</th>
<th>Laboratory-confirmed non-COVID (n=33)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>2019-nCoV identification</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Suspected chest CT signs</td>
<td>20/20</td>
<td>20/33</td>
</tr>
<tr>
<td>First time SARS-CoV-2 PCR positive</td>
<td>14/20</td>
<td>0/33</td>
</tr>
<tr>
<td>Second time SARS-CoV-2 PCR positive</td>
<td>3/6</td>
<td>0/33</td>
</tr>
<tr>
<td>mNGS positive for SARS-CoV-2</td>
<td>20/20</td>
<td>0/33</td>
</tr>
<tr>
<td><strong>Other respiratory infection pathogens</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Direct antigen Flu A+B test positive</td>
<td>0/20</td>
<td>0/33</td>
</tr>
<tr>
<td>Multiplex PCR positive for other pathogens</td>
<td>5/20</td>
<td>7/20</td>
</tr>
<tr>
<td>mNGS positive for other pathogens</td>
<td>11/20</td>
<td>23/33</td>
</tr>
</tbody>
</table>

JW Ai, HC Zhang et al.
medRxiv2020.02.13.20022673; doi: https://doi.org/10.1101/2020.02.13.20022673
Co-infections in the COVID-19 patients

NCP Cases with co-infection status

Non NCP cases

- novel coronavirus (2019-nCoV) pneumonia
- non-novel coronavirus (2019-nCoV) pneumonia

- Rhinovirus/Enterovirus
- Influenza B
- Respiratory Syncytial Virus
- Haemophilus parainfluenzae
- Candida albicans
- Klebsiella aerogenes
- Non-co-infection cases

Chest CT alone could not precisely diagnose COVID-2019 due to sometimes similar radiological presentations.
Recommended diagnostic flow diagram (1).

Suspected NCP patients → Collect respiratory specimens

PCR for other pathogens/Direct antigen test (if applicable)

First time SARS-CoV-2 PCR

Positive

Negative

Second time SARS-CoV-2 PCR
Recommended diagnostic flow diagram (2).

- First step: Second time SARS-CoV-2 PCR
  - Positive: Send to Repeated sampling PCR
  - Negative: Clinical highly suspected/critical cases
    - Repeated sampling PCR
    - Different sampling site
    - mNGS
      - National Certified Third Party Agency
        - Positive: Laboratory confirmed NCP
        - Negative: Rule out
Timely diagnosis and timely quarantine

The mean incubation period is 6.4 days (95% CI 5.3 to 7.6), and the mean onset-admission interval was 5.5 days (95% CI, 5.1 to 5.9, SD 3.5) in Shanghai.

Sources: HZ Lu, JW Ai, WH Zhanget al. medRxiv
Early control of the local transmission is the key to stop the diseases spreading.

Shanghai’s data showed effective control of the local cases (green bars).

Sources: HZ Lu, JW Ai, WH Zhanget al. medRxiv
Early control of the local transmission is the key to stop the diseases spreading.

Italy’s data showed epidemics mainly due to local transmission.

Sources: Huashan Hospital
Treatment options for COVID-19
Antiviral treatment

- Currently, no effective antiviral treatment has been identified

- Several drugs, including Arbidol tablets, Lopinavir/Ritonavir hydroxychloroquine sulfate, and Remdesivir are currently in clinical trial.

- But in the meantime, compassionate drug could be used under permitted situations.
Sufficient respiratory support is the fundamental treatment

In Wuhan

<table>
<thead>
<tr>
<th>Clinical characteristics</th>
<th>All patients</th>
<th>With ARDS, No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Without ARDS, No. (%) (n = 117)</td>
<td>With ARDS, No. (%) (n = 84)</td>
</tr>
<tr>
<td>Treatment in hospital</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oxygen therapy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nasal cannula</td>
<td>81 (69.2)</td>
<td>17 (20.2)</td>
</tr>
<tr>
<td>NMV</td>
<td>0</td>
<td>61 (72.6)</td>
</tr>
<tr>
<td>IMV</td>
<td>0</td>
<td>5 (6.0)</td>
</tr>
<tr>
<td>IMV with ECMO</td>
<td>0</td>
<td>1 (1.2)</td>
</tr>
</tbody>
</table>

As of February 13, 2020, 144 of the total 201 patients (71.6%) were discharged from the hospital. The median hospital stay was 13 days (IQR, 10-16 days), and 13 (6.5%) patients were still hospitalized. Of the entire cohort, 84 (41.8%) patients developed ARDS, 53 (26.4%) were admitted to the intensive care unit, 67 (33.3%) received mechanical ventilation, and 44 (21.9%) died. Among the 67 patients who received mechanical ventilation, 44 (65.7%) died, 14 (20.9%) were discharged from the hospital, and 9 (13.4%) remained hospitalized. The median time

In Shanghai

All 17 ARDS patients received invasive mechanical ventilation, 6 of whom were treated with ECMO. 4 ARDS (23%) patients died. 6 ARDS patients (35%) were discharged.

Among ARDS patients:

- Invasive mechanical ventilation support rate: 7% (Wuhan) vs. 100% (Shanghai)
- Mortality rate: 52.4% (Wuhan) vs. 23% (Shanghai)
Risk factors associated with COVID-19 progression

- Recently studies show that organ and coagulation dysfunction (e.g., higher lactate dehydrogenase and D-dimer) are crucial factors during ARDS progression to death.
Potential effective treatment

ECCHYMOsis in severe type of COVID-19 patients

hypercoagulable phase of DIC. It is believed that COVID-2019 can activate coagulation cascade through various mechanisms, leading to severe hypercoagulability. Early anticoagulation may block clotting formation and reduce microthrombus, thereby reducing the risk of major organ damages [5,6].

Moreover, there are studies supporting the use of corticosteroids at low-to-moderate dose in patients with coronavirus infection. For example, in a retrospective study of 401 patients with SARS,4 proper use of corticosteroids was found to reduce mortality and shorten the length of stay in hospital for critically ill patients with SARS without causing secondary infection and other complications. Relevant

However, no strong clinical evidence of anticoagulant or corticosteroids has been observed.
Other treatments

Life support for critically ill patients is crucial, and the right time frame for nasal cannula or mask oxygen inhalation, high-flow nasal cannula oxygen therapy, invasive mechanical ventilation and extracorporeal membrane oxygenation (ECMO) should be determined.

Organ support, hemodynamic stability, nutritional support, analgesia and sedation should be maintained according to the situations in individual patients.
Prognosis

- The overall mortality rate of COVID-19 is around 3-4% (<1% in Shanghai)
- The main risk groups are elderly, or patients with previous underlying diseases
- Young people, although has a relatively lower chance or progressing to severe disease state, should be aware of the fact that they could easily transmit the diseases to others if infected.
How to protect medical personnel

- Qualified and standardized process design were needed firstly, including doctor-patient access, medical personnel access, etc.

- Secondly, appropriate personal protective equipment: medical protective masks, isolation gowns, goggles or visors, double-layer gloves, double-layer shoe covers, etc.;

- Comprehensive masks or positive pressure breathing masks are recommended when aerosol is easy to spread in short distance.

- Disinfection and isolation: negative pressure ward as far as possible, the use of hydrogen peroxide to disinfect the environment at least every 4 hours to wipe the surface of objects, and the use of hydrogen peroxide to disinfect the environment at the end.
COVID-19 diagnostics (新冠病毒的检测 1)

- What is the time window between infection and test positive?
  - 感染新冠病毒多久后可以检测出阳性？

- For general public, what are the criteria to request a SARS-CoV-2 test? For healthcare workers?
  - 对于普通民众，满足什么样的条件就可以进行新冠病毒的测试？对于医护人员呢？

- ***What are the pros and cons of PCR-based test Vs antibody-based test? False positive and false negative rate?***
  - 新冠病毒PCR检测和抗体检测各有那些优缺点？假阳性和假阴性率？
COVID-19 diagnostics (新冠病毒的检测 2)

- How to prevent viral RNA degradation during sample processing?
  - 新冠病毒是RNA病毒，如何保证检测样品中的病毒RNA不会降解掉?

- People who are self-quarantined for 14 days at home, should they be tested? If yes, when and how frequent?
  - 居家隔离14天的人，需要做新冠病毒测试吗？要做几次呢？

- What is the risk of infection for pregnant woman and infant compared with other demographic groups? If infected, what are the treatment options?
  - 孕期妇女和婴儿感染新冠病毒的风险和其他群体有何不同？治疗上有那些方案?
COVID-19 progression (病情/疫情的进展)

- From mild to severe symptoms, how long will it take?
  - 一般需要多长时间，新冠病毒感染轻症会发展成重症新冠肺炎？

- Why people with underlying medical conditions are at high risk?
  Young age but with underlying conditions are also at high risk?
  - 为何有基础疾病的人是新冠肺炎的高风险？有基础疾病的年轻人呢？

- ***At large population level, do you observe the attenuation of the infectivity or pathogenicity of SARS-CoV-2 over time?
  - 从群体流行病学来看，是否观察到新冠病毒的毒力在逐渐减弱？
COVID-19 treatment (新冠病毒/肺炎的治疗 1)

- **Ibuprofen Vs acetaminophen, which one is better to treat fever at home for mild COVID-19 patient?**
  - 家庭治疗新冠病毒感染引起的发烧，布洛芬与对乙酰氨基酚谁更合适？（法国报道布洛芬不建议使用）

- **Literature report that ARB inhibitor like Losartan can increase cell surface ACE2 expression. Do you observe people who are taking ARBi showing a higher chance of SARS-CoV-2 infection? How about use Losartan to reduce lung inflammation in COVID-19?**
  - 文献报道，像氯沙坦这样的ARB抑制剂（一种降血压药物）可以增加细胞表面ACE2的表达。您是否观察到服用氯沙坦的人感染新冠病毒的机会更高？从另一个角度，使用氯沙坦能减轻COVID-19中的肺部炎症吗？
COVID-19 treatment (新冠病毒/肺炎的治疗 2)

- What is the percentage of recovered patients showing detectable neutralizing antibodies against SARS-CoV-2? What type of antibodies? What is the efficacy against COVID-19?
  - 康复患者中有可检测出的中和性抗SARS-CoV-2抗体的百分比是多少？什么类型的抗体？抗COVID-19有什么功效？

- Will upcoming summer slow down global pandemic of COVID-19?
  - 即将到来的夏季会不会减缓新冠病毒的疫情？
hydroxychloroquine for treatment (羟氯喹用于治疗)

- **How to use hydroxychloroquine for COVID-19 treatment? Dose and frequency? Efficacy and side effects?**
  - 请问羟氯喹是否可以用于治疗新冠？怎样用？疗效和副作用是什么？

- **How about hydroxychloroquine + azithromycin or + Zinc?**
  - 羟氯喹和阿奇霉素或者锌合用呢？

- **What are the possible mechanisms of action of hydroxychloroquine for COVID-19?**
  - 羟氯喹治疗新冠肺炎可能作用机制有哪些？
Protection of Healthcare Workers (医护人员的防护 1)

- How important it is to cover head/neck/shoes when treating COVID patients?
  - 在治疗新冠病人的时候，覆盖头，脖子，以及鞋子有多重要。

- How often are HCWs infected from the virus?
  - 医护人员被感染的几率/可能性有多高？

- Is regular surgical mask sufficient for HCWs to prevent COVID-19 under mild patient Vs severe patient
  - 对于轻症和重症的病人，普通的外科手术口罩足够防护吗？

- Are you routinely testing healthcare workers who are exposed to COVID+ patients?
  - 接触新冠病人的医护人员需要经常做病毒感染测试吗？
Protection of Healthcare Workers (医护人员的防护 2)

- ***With limited supply of personal protective equipment (PPE), what is a minimum workflow to preserve PPE while still protect workers?
  - 在医院防护用品不足的情况下，能不能建议一个基本的工作流程来保护医护人员

- ***Can COVID-19 be transmitted by air droplet/airborne, in closed spaces, such as elevator, waiting room?
  - 新冠病毒空气可以传染是真的吗？比如在医院，电梯，侯诊室等人多密闭的空间

- ***At US, healthcare workers go home after work. What procedure need to be done to prevent spreading the virus to family members?
  - 医务人员需要跟家属隔离吗：美国照顾新冠患者的医护人员在医院没有休息室的，下班后都会回家。有什么清洁程序应该做？个人卫生方面要注意什么？应该自觉遵守居家隔离原则，与家人严格分开吗？
Protection of Healthcare Workers (医护人员的防护 3)

- For hospital department that does not directly interact with COVID-19 patients, can healthcare workers use reduced PPE?
  - 医院里不直接接触新冠病人的科室，医护人员是不是可以少带或不带个人防护?

- For healthcare workers that interact with COVID-19 patients, what need to be done before eating and drinking?
  - 医护人员中途午休息时间应该注意什么？预先需要清洁面部吗？怎么清洁才安全？
Discharge and follow up of COVID-19 patients (康复出院和后续)

- What is the procedure to discharge COVID-19 recovered patients? Do they need to self-quarantine at home for 14-days? Is there a possibility of viral rebound?
  - 新冠肺炎病人治愈出院的流程是怎样的？出院后需要在家隔离14天吗？会复发吗？

- If a patient survived severe COVID-19, will his/her lung suffer long term injury? Fibrosis?
  - 痊愈出院的新冠肺炎病人，肺会不会有永久性的损伤或者纤维化的危险？