

**Diagnostic (chest CT, chest X-ray, bronchoscopy, PCR test, etc.)**

**1. How many of these patients with abnormal chest CT had a 'normal' chest x-ray? Do we have data on that?**

A: We have no data on that now.

**2. Was bronchoscopy performed for some of these patients and how did performance of PCR change based on sampling site if so?**

A: No comparison has been reported for the positive rate of SARS-CoV-2 RNA detection between swabs and bronchoalveolar lavage fluid (BALF).

In previous study, the positive rate of SARS-CoV-2 RNA detection is higher in nasopharyngeal swab than throat swabs(1. Lirong Zou et al. N Engl J Med.2020 Feb 19[Online ahead of print]), and the positive rate in anal swabs was higher than nasopharyngeal swab in late stage of infection (2.Wei Zhang, et al, Emerg Microbes Infect. 2020, 9 (1), 386-389). In a research of 176 lab-confirmed mild patients with COVID-19 from a designated infectious hospital in Shenzhen, China, the total positive rate of SARS-CoV-2 RNA was highest in sputum (82.2%) compared to nasopharyngeal (72.1%) and oropharyngeal swab (61.3%) at early stage of disease (0-7 days from illness onset)(3.Yang Y et al. medRxiv 2020.)

In our hospital, a 69 year old man with pneumonia was finally diagnosed with COVID-19 at the fifth SARS-CoV-2 RNA test, which showed a positive result in bronchoalveolar lavage fluid. Prior to this, the RNA test was run three times with nasopharyngeal swab specimen and once with sputum, which all came back negative (4. Xiaojing Wu et al. Emerg Infect Dis. 2020.26 (6)).

**3. How long would you wait before doing a second PCR test?**

A: If you want to confirm the SARS-CoV-2 infection in highly suspect patients and the former result of RNA test was negative, the re-examination should be done as soon as possible.

If you want to determine whether the patients could be discharged, the re-examination of SARS-CoV-2 RNA could be done every other day, after

absence of fever for at least 3 days, substantial improvement in both lungs in chest CT and clinical remission of respiratory symptoms.

When effective antiviral drugs are available in practice in the future, the PCR test could be done after antiviral therapy is finished to monitor the effect of treatment, and/or to determine the duration of antiviral therapy.

***4. Noted that everyone with pneumonia was admitted, I think it said - was that by CT diagnosis, and was that because of concern for potential rapid progression? How we can safely decide who, if anyone with pneumonia from SARS-COV-2 could be treated at home - can we safely use pneumonia severity index (PSI) or maybe not?***

A: In Wuhan, China, all cases confirmed with COVID-19 including patients with pneumonia were admitted for isolation. Criteria for admission for Mobile cabin hospitals were: 1) age < 65 yrs; 2) SpO<sub>2</sub> > 93% (room air); 3) no influenza infection; and 4) being able to take care of oneself. Other cases were admitted to designated hospitals.

According to our data (only including inpatients in designated hospitals), the AUC of the ROC curve of SOFA, PSI, CURB-65 and qSOFA for predicting in-hospital death was 0.956, 0.911, 0.779 and 0.779. The AUC of SOFA score and PSI has no statistical significant difference. But the PSI seems relative more complex for use in emergency department. More research should be done to investigate how to identify the patients with poor outcome and with low PSI score admission.

***ICU/Medical-Related (ARDS, ventilation, ECMO, etc.)***

***5. Top 10 things that Dr. Peng & colleagues think we need to know and/or the top 10 lessons from your experiences in ICU?***

***6. What are the thresholds for ICU admission?***

A: In guideline of management of COVID-19 in China, the disease was divided into four categories according to illness severity: mild, moderate, severe and critically ill status. Critically ill status is diagnosed when patients need invasive mechanical ventilation, occurrence shock or needs other organ support therapy. I think the criteria of critically ill status could

be regarded as the thresholds for ICU admission.

The ICU admission threshold for CAP may also be helpful.

Validated definition includes either one major criterion or three or more minor criteria:

**Minor criteria:**

- 1) Respiratory rate > 30 breaths/min PaO<sub>2</sub>/FIO<sub>2</sub> ratio < 250
- 2) Multilobar infiltrates Confusion/disorientation
- 3) Uremia (blood urea nitrogen level > 20 mg/dl)
- 4) Leukopenia\* (white blood cell count, 4,000 cells/ml)
- 5) Thrombocytopenia (platelet count, 100,000/ml)
- 6) Hypothermia
- 7) Hypotension requiring aggressive fluid resuscitation

**Major criteria**

- 1) Septic shock with need for vasopressors
- 2) Respiratory failure requiring mechanical ventilation

***7. What is your experience with caring for patients under the age of 18 years—how many have been mechanically ventilated, survived died?***

A: Most patients in the hospital where I worked were adults, so the experience for children and adolescents was limited. According to previous study, the rate of intubation in adult patients admitted to hospital was 10%—17%. The fatality of these patients has not been well established. In the latest research, we included all inpatients with COVID-19 and with definitive outcomes (dead or discharged) in two designated hospitals as of Jan 11, 2020. 31 of 32 patients with invasive ventilation were dead.

***8. Besides ARDS, is there significant other organ injury with COVID-19, in particular ventricular dysfunction, pulmonary hypertension, encephalopathy, secondary bacterial co- infection?***

A: Sepsis, heart failure, coagulopathy, acute cardiac injury, acute kidney injury, secondary infection, hypoproteinaemia, acidosis were also observed in severe COVID-19. In our latest study, the median time for illness onset was 10.0 days for sepsis, 12.0 days for ARDS, 14.5 days for acute cardiac injury, and 17.0 days for secondary infection in non-survivors.

***9. Are there any therapies for the critically ill patients with ARDS that appeared beneficial or harmful?***

***10. Any restrictions on rescue therapies for refractory hypoxemia in ARDS?***

***11. How often did you obtain lower respiratory samples (and with what technique), and how often was an upper sample negative but lower respiratory tract sample positive?***

A: We have no data for the rate. In a research of 176 lab-confirmed mild patients with COVID-19 from a designated infectious hospital in Shenzhen, China, the total positive rate of SARS-CoV-2 RNA was highest in sputum (82.2%) compared to nasopharyngeal (72.1%) and oropharyngeal swab (61.3%) at early stage of disease (0-7 days from illness onset)(3. Yang Y et al. medRxiv 2020.)

***12. Any strategies on how to manage the \*cardiac complications\* of the ICU patients? Anything different than the usual?***

***13. Can you clarify the rate of co-infection with another virus for patients with confirmed COVID-19?***

A: We have no data about it.

***14. Any guidance on using not CCM-trained providers for critical illness?***

---

**【Ventilation and ECMO】**

***15. Definition of “time-limited trial” of mechanical ventilation in this context (i.e. when does death seem inevitable?)***

***16. What is the survival rate for ECMO patients? What is the true survival of ventilated patients?***

***17. What is average time on ECMO? Average age of ECMO patients?***

**18. What proportion of ECMO patients received VV vs. VA ECMO?**

**19. For the small number of patients requiring ECMO or prolonged mechanical ventilation, how did you decide on criteria (limited resource)?**

**【immunosuppressed patients/cancer patients】**

**20. Any data on characteristics and outcomes in immunosuppressed patients (transplant patients, cancer patients etc).**

A: No data about these patients now.

**21. Do you have information regarding clinical presentation and outcomes among cancer patients including stem cell transplant recipients? Interested in knowing whether clinical symptoms/presentations vary compared to general medical population.**

A: No data about these patients now.

### **Health care workers protection**

22. What are your lessons learned on the optimal and practical personal protective (PPE) equipment needs for the health care providers for patients in the ICU? In particular, should we assume full airborne precautions, or is droplet precaution sufficient?

23. What is the optimal number of times to don and doff PPE for the ICU nurses and physicians (only once, or can donning and doffing be learned to be done very safely and thus as needed)? *\*\*don – put on; doff – take off*

24. What is the rate of infection of healthcare workers in the ICU as more experience with the disease has evolved? Overall, what percent of the health care workers became positive for the virus?

25. What is the optimal shift rotation, in terms of number of hours, for nurses and physicians in the ICU?

26. What are health care workers advised to wear for general work in the ICU? In other words, are regular clothes allowed or do the staff wear hospital-issued clothing?

27. For the clinical laboratories doing testing, what level of precaution or PPE would be appropriate for preanalytical and analytical personnel?
28. What kind of PPE did your staff wear for a) intubation, b) NIV (Noninvasive ventilation), and c) HFNC (High flow nasal cannula) ?
29. What were the best ways to prevent risks for health care workers, especially once the usual PPE supplies were exhausted?

### **Treatments / Experimental Treatments / Clinical Trials**

**30. Do you have any experience with experimental medical therapies, such as chloroquine (氯喹), oseltamivir (奥司他韦), remdesivir(瑞德西韦)?**

A: The latest study documents the antiviral effect of chloroquine or hydroxychloroquine in vitro (5.Yao X, et al. Clin Infect Dis 2020.). But I have no experience of using chloroquine. The neuraminidase inhibitors are NOT useful in treatment of COVID-19, for SARS-CoV-2 virus doesn't have neuraminidase in the capsule.

Right now, there are two ongoing remdesivir trials. Both are randomized, double-blind, placebo-controlled, multicenter studies to evaluate the efficacy and safety of Remdesivir in hospitalized adult patients with COVID-19. Remdesivir 2 is for severe patients, and remdesivir 1 is for mild-moderate patients with pneumonia. There has been no SAE occurred in these two trials. But, the effect of Remdesivir is still unknown, for the double-blind RCT trial is still ongoing.

**31. Have you tried Xygris the old sepsis drug?**

A: To my knowledge, Xygris (drotrecogin $\alpha$ ) was found ineffective in treatment of sepsis in previous RCT study, and this drug was not available in China.

**32. Which drugs are recommended for anticoagulation?**

A: In our ward, low-molecular-weight Heparin is given for patients with high risk of thrombus and low risk of bleeding.

**33. For Dr. Cao - Are you using therapeutic or prophylactic anticoagulation on these patients? IF therapeutic - is this only in patients with elevated D-dimer levels?**

A: The illness of patients admitted to our designated hospital is relatively severe. All patients with high risk of venous thromboembolism (VTE) and low risk of bleeding would receive prophylactic anticoagulation therapy according to weight. The risk of VTE and bleeding was evaluated based on the guideline of management and prophylactic treatment of venous thromboembolism. If the D-Dimer increased significantly, the dosage of Low-molecular-weight Heparin may be adjusted, but the optimal dosage and duration of anticoagulation treatment needs further investigation for COVID-19 patients with high level of D-Dimer.

**34. What is our current knowledge of the existence of the virus remaining in the body even after patients recover? Is there any evidence the virus, or the virus gene retains in human body? Which leads to those diseases re-occurrence on some patients after they recover?**

A: I also heard about the SARS-CoV-2 RNA was detected in discharged patients. In China, the criteria for discharging are as following:

- 1) absence of fever for at least 3 days;
- 2) substantial improvement in both lungs in chest CT;
- 3) clinical remission of respiratory symptoms;
- 4) two throat-swab samples return negative for SARS-CoV-2 RNA obtained at least 24 h apart.

In our latest study, the median duration of viral shedding in patients with SARS-CoV-2 pneumonia is 20 days, and could prolong as long as 37 days in survivors. I think the so-called “re-occurrence” was a misunderstanding of the information. The positive rate of SARS-CoV-2 RNA detection in upper respiratory tract is relative low (1. Lirong Zou et al. N Engl J Med. 2020 Feb 19[Online ahead of print]). I think the so-called “re-occurrence” is due to false negative result of SARS-CoV-2 RNA detection. More over, although the symptoms of these patients were relieved upon discharge, but these patients may not have completely recovered from the illness. In our study, 45% patients still have coughing at discharge. So, whether virus could remain in the body after complete recovery needs further investigation.

***35. Have you detected any mutations in the virus?***

A: The study from Peking University (6.Xiaolu Tang et al. National Science Review. 03 March 2020) documents that the viruses evolved into two major types (designated L and S). S type was found to be the ancestral version and L type more prevalent in the early stages of the outbreak. S type might have increased in relative frequency due to relatively weaker selective pressure now.

***36. Are there reliable data regarding the effectiveness of traditional herbal therapy in treating COVID-19?***

A: I am not familiar with the field.

**Hospital Resources Management**

***37. For hospitals that have other emergency service requirements (like trauma centers), how was this handled with regards to ICU capacity?***

***38. How to manage excess inpatient volumes - including limiting eligibility for ICU care, cancelling semi-elective treatments and surgeries/procedures, and arranging overflow rooms for respiratory failure. Did you alter the administration of chemotherapy?***

***39. Was there consideration of regional distribution of patients to preserve some ICU capability?***

***40. What did you do for elective surgery? Did you cancel all elective cases? How did you prioritize other services?***

***41. It takes us 2 hours to sanitize the CT scanner after a COVID patient is imaged. Did you find any high-throughput ways to decrease that?***

***42. How many hospital/ICU beds per capita in Shanghai?***

***43. Which patients did you allocate to air-vented rooms vs negative pressure?***

**44. Were there any other resources that were unexpectedly consumed?**

**45. How many patients can be safely cared for by a physician and how did you structure the care teams (e.g. supervising specialist, non-specialists, etc.)?**

**46. What changes in usual practice did you adopt to enhance efficiency? (e.g. frequency of VS, labs, POC testing, bedside US)**

**47. How did you structure provider rotation to mitigate fatigue/burnout?**

**48. Do you think US current control measures are effective? What can the US learn from China in order to have enough testing?**

1. Lirong Zou, Feng Ruan, Mingxing Huang et al. SARS-CoV-2 Viral Load in Upper Respiratory Specimens of Infected Patients. *N Engl J Med*. 2020 Feb 19 [Online ahead of print]. DOI: 10.1056/NEJMc2001737
2. Wei Zhang, Rong-Hui Du, Bei Li, et al. Molecular and Serological Investigation of 2019-nCoV Infected Patients: Implication of Multiple Shedding Routes. *Emerg Microbes Infect*. 2020, 9 (1), 386-389.
3. Yang Y, Yang M, Shen C, et al. Evaluating the accuracy of different respiratory specimens in the laboratory diagnosis and monitoring the viral shedding of 2019-nCoV infections. *medRxiv* 2020.
4. Xiaojing Wu, Ying Cai, Xu Huang et al. Co-infection With SARS-CoV-2 and Influenza A Virus in Patient With Pneumonia, China. *Emerg Infect Dis*. 2020.26 (6) [Online ahead of print]
5. Xueting Yao, Fei Ye, Miao Zhang et al. In Vitro Antiviral Activity and Projection of Optimized Dosing Design of Hydroxychloroquine for the Treatment of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2). *Clin Infect Dis*. 2020 Mar 9 [Online ahead of print]
6. Xiaolu Tang, Changcheng Wu, Xiang Li et al. On the origin and continuing evolution of SARS-CoV-2. 2020. [accepted]. DOI: 10.1093/nsr/nwaa036