COVID-19: Update from China

• Slides from the 18 March 2020 briefing from the Chinese Cardiology Association to members of the American Cardiology Association
### Diagnostic criteria of COVID-19—-Suspected cases

<table>
<thead>
<tr>
<th>Suspected cases</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Epidemiological history (≤14 days)</strong></td>
</tr>
<tr>
<td>travel /residence in Wuhan and its surrounding areas, or other communities where COVID-19 has been found</td>
</tr>
<tr>
<td>contact with COVID-19 patients</td>
</tr>
<tr>
<td>Contact with patients with fever or respiratory symptoms and from Wuhan and its surrounding areas, or from communities where COVID-19 has been found</td>
</tr>
<tr>
<td>Clustered cases</td>
</tr>
</tbody>
</table>

- Any one criteria of Epidemiological history + Any two Clinical symptoms
- All three clinical symptoms
## Diagnostic criteria of COVID-19——Confirmed cases

**Confirmed cases**

<table>
<thead>
<tr>
<th>Etiological or serological evidences</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nucleic acid testing</td>
</tr>
<tr>
<td>- SARS-CoV-2 RNA was positive detected by real time RT-PCR</td>
</tr>
<tr>
<td>- Viral gene sequence is highly homologous to known new coronaviruses</td>
</tr>
<tr>
<td>Serum antibody testing</td>
</tr>
<tr>
<td>- SARS-CoV-2 specific IgM and IgG are positive in serum</td>
</tr>
<tr>
<td>- SARS-CoV-2 specific IgG is detectable from negative to positive</td>
</tr>
<tr>
<td>- SARS-CoV-2 specific IgG antibody titer shows a 4-fold or higher change between the two sets of serum samples from acute and recovery phase</td>
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</tbody>
</table>

**Suspect cases + one of etiological or serological evidences**
Clinical features of COVID-19 patients

<table>
<thead>
<tr>
<th>Symptoms and complications</th>
<th>N%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fever</td>
<td>98%</td>
</tr>
<tr>
<td>Cough</td>
<td>76%</td>
</tr>
<tr>
<td>Myalgia or fatigue</td>
<td>44%</td>
</tr>
<tr>
<td>Sputum production</td>
<td>28%</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>3%</td>
</tr>
<tr>
<td>WBC ≤ 10 × 10⁹/L</td>
<td>70%</td>
</tr>
<tr>
<td>Lymphocytopenia</td>
<td>63%</td>
</tr>
<tr>
<td>ALT &gt; 40 U/L</td>
<td>37%</td>
</tr>
<tr>
<td>Cr &gt; 133 mmol/L</td>
<td>10%</td>
</tr>
<tr>
<td>LDH &gt; 243 U/L</td>
<td>73%</td>
</tr>
<tr>
<td>Hypersensitive troponin I &gt; 28 pg/ml</td>
<td>12%</td>
</tr>
<tr>
<td>Procalcitonin &lt; 0.1 ng/ml</td>
<td>69%</td>
</tr>
<tr>
<td>Acute respiratory distress syndrome</td>
<td>29%</td>
</tr>
</tbody>
</table>

Symptoms and complications N%

- Acute cardiac injury 12%
- Acute kidney injury 7%
- Septic shock 7%
- Secondary infection 10%

Abnormal coagulation is common in severe COVID-19

D-Dimer $> 1$ug/ml was independent risk factor of in-hospital death

- Significantly increased D-dimer and FDP were associated with poor prognosis
- Vascular endothelium inflammation Extensive intravascular microthrombosis on autopsy
- Vascular endothelial cells express high levels of ACE2

Anticoagulation therapy should be initiated for severe COVID-19 patients if otherwise contraindicated.

Treatment options for severe or critical COVID-19

- Respiratory support
- Circulatory support
- Renal replacement therapy
- Blood purification treatment
- Convalescent plasma treatment
- Immunotherapy
- Other therapeutic measures

18 March 2020
Antiviral interventions

- So far, no specific antiviral against SARS-CoV-2 has been proved
- Clinically evaluated drugs:
  - Lopinavir/ritonavir monotherapy (LOTUS China, ChiCTR2000029308): completed, manuscript accepted, online tomorrow
  - Promising results
  - CAP China Remdesivir 1 (mild-moderate pneumonia, NCT04252664): ongoing
  - CAP China Remdesivir 2 (severe-critical pneumonia, NCT04257656): ongoing

Ennie de Wit et al. Nature Reviews Microbiology 2016; 14, 523–534
Timothy P Sheahan; Nat Commun 2020; 11 (1), 222
Yeming wang, et al. Trial, 2020, under peer review
CAP-China Remdesivir trials on going for COVID-19

Remdesivir:
First dosage: 200mg iv qd×1days;
Continuous 100mg qd×9days
Placebo: 50ml qd×10days

2:1 randomization

Standard care + Remdesivir
Standard care + Placebo

Total course of treatment: 10 days

≤ 12 days Screen enroll Follow up
Illness onset hospitalization

24 h Day 0 Day 1 Day 3 Day 5 Day 7 Day 10 Day 14 Day 21 Day 28
Primary outcome: Clinical improvement on day 28
Secondary outcome: The time from randomization to clinical improvement

The clinical trail of Remdesivir treatment for severe COVID-19 is on going
Antiviral for COVID-19: other potential choices

- Alpha-interferon: 5 MU, atomization inhalation twice daily
- Ribavirin: used together with interferon or lopinavir/ritonavir, 500 mg twice or three times of intravenous injection daily, no longer than 10 days
- Chloroquine phosphate: 500 mg bid for 7 days for adults aged 18-65 with body weight over 50 kg; 500 mg bid for Days 1&2, and 500 mg daily for Days 3-7 for adults with body weight below 50 kg
- Arbidol: 200 mg three time daily for adults, no longer than 10 days
- Convalescent plasma treatment: infusion dose 200-500ml (4-5 ml/kg) \( \times 2 \)
- Favipiravir
Dilemma of ARB/ACEi

- Letter from Prof. Giovanni de Simone, Chair, Council on Hypertension, European Society of Cardiology
  - Anti-RAS meds of course reduce angio-II activity, which is good for lung inflammatory response.
  - However, too much inhibition of angio-II might increase ACE2 activity, because angio-II increase ACE2 cleavage through AT1R-activated TNF-alfa-ACE, and this might not be good for the COVID-19 action.
- Bin Cao' response to Prof. Giovanni de Simone
  - In our cohort, 48% (26/48) non-survivors had hypertension, whereas the percentage of hypertension was only 23% (32/137) in survivors. The OR for hypertension in ANOVA is 3.05 (1.57-5.92).
- No definite answer to the question of ARB/ACEi

Use of corticosteroid is still controversial

- Only for patients with rapid progressive deterioration oxygenation, radiology imaging and excessive inflammation
- Contraindications: allergy; un-controlled diabetes; uncontrolled hypertension; glaucoma; GI bleeding; immunodepression; lymphocyte less than 300/ul; severe bacterial and/or fungal infections
- Short term, 3-5 days
- Low-moderate dosage
  - no more than methylprednisolone 1-2 mg/kg/day

Hypotheses of cardiac injury in COVID-19

- **2019-nCoV infection**
  - **ACE2-mediated direct damage**
    - Increased affinity to ACE2
    - Reduced ACE2 expression
    - Dysregulated RAS
  - **Hypoxia-induced myocardial injury**
    - Oxidative stress
    - Intracellular acidosis
    - Mitochondrial damage
  - **Cardiac microvascular damage**
    - Perfusion defect
    - Vessel hyperpermeability
    - Angiосasm
  - **Systemic inflammatory response syndrome**
    - Cytokine storm
    - Dysregulated immunocyte
    - Uncontrolled inflammation

**Acute cardiac injury**

Yundai Chen. Chin J Pathophys. 2020;
Underlying cardiac implications of COVID-19: cardiac injury in clinical trials

- Common complications among the 138 patients from Zhongnan Hospital of Wuhan University included shock (12 [8.7%]), ARDS (27 [19.6%]), arrhythmia (23 [16.7%]), and acute cardiac injury (10 [7.2%]).

<table>
<thead>
<tr>
<th>Complications</th>
<th>Total (N = 138)</th>
<th>ICU (n = 36)</th>
<th>Non-ICU (n = 102)</th>
<th>P Valuea</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shock</td>
<td>12 (8.7)</td>
<td>11 (30.6)</td>
<td>1 (1.0)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Acute cardiac injury</td>
<td>10 (7.2)</td>
<td>8 (22.2)</td>
<td>2 (2.0)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Arrhythmia</td>
<td>23 (16.7)</td>
<td>16 (44.4)</td>
<td>7 (6.9)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>ARDS</td>
<td>27 (19.6)</td>
<td>22 (61.1)</td>
<td>5 (4.9)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>AKI</td>
<td>5 (3.6)</td>
<td>3 (8.3)</td>
<td>2 (2.0)</td>
<td>.11</td>
</tr>
</tbody>
</table>

*JAMA. doi:10.1001/jama.2020.1585*
Management strategy for severe patients with COVID-19 and CVD

- Cardiac injury mainly occurs in severe patients, and mortality in severe cases accounts for as high as 49%
- SARS-CoV2 infection maybe an initiating factor, preventing transition to severe cases is crucial

Clinical warning indexes

Mild, normal cases
- Lymphocytes decrease progressively
- Inflammatory cytokines such as IL-6, CRP increase progressively
- Lactate presents an ongoing increase
- Pulmonary lesions progress rapidly in a short period

Severe cases
Decreased pericardial adipose tissue is positively associated with the severity of COVID-19

- The elevation of TnI in critical patients is statistically significant compared with other groups.
- CT threshold attenuation value of pericardial adipose tissue (EAT) decreased in the critical, severe and mild group, and they were lower than the light group.

<table>
<thead>
<tr>
<th></th>
<th>Light</th>
<th>Mild</th>
<th>Severe</th>
<th>Critical</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (year)</td>
<td>31.00 (48.8%)</td>
<td>24.97 (78.05%)</td>
<td>68.25 (9.75%)</td>
<td>70.67 (7.32%)</td>
</tr>
<tr>
<td>White blood cell count</td>
<td>3.07</td>
<td>4.15 (3.40-5.56)</td>
<td>5.85 (4.50-12.87)</td>
<td>9.40 (2.63-12.16)</td>
</tr>
<tr>
<td>lymphocyte percentage</td>
<td>34.70</td>
<td>28.32 (22.35-37.35)</td>
<td>16.60 (11.4-16.4)</td>
<td>12.70</td>
</tr>
<tr>
<td>C-reactive protein (mg/L)</td>
<td>1.20</td>
<td>1.41 (2.73-23.05)</td>
<td>5.72 (3.80-9.80)</td>
<td>191.00 (121.90-211.00)</td>
</tr>
<tr>
<td>Troponin I (ng/mL)</td>
<td>0.01</td>
<td>0.01</td>
<td>0.10</td>
<td>0.54 (0.05-5.90)</td>
</tr>
<tr>
<td>Creatinine (mg/dL)</td>
<td>53.00</td>
<td>69.00 (60.71-71.75)</td>
<td>78.00 (40.00-116.00)</td>
<td>129.00</td>
</tr>
<tr>
<td>SPO2 (%)</td>
<td>97/95(92-97.4)</td>
<td>90.5 (88.25-91.5)</td>
<td>64/60 (60-76)</td>
<td></td>
</tr>
</tbody>
</table>

light (a), mild (b), severe (c) and critical (d)
Coronavirus fulminant myocarditis

- Male, 37y, Chest pain and dyspnea for 3 days
- X-ray showed enlargement of the heart (A)
- Chest CT indicated pulmonary infection (B,C)
- ECG showed III and AVF ST segment elevation (D,E)
- Coronary angiography revealed no stenosis
- Test: TnT >10000 ng/L; CK-MB 112.9 ng/L
- Echocardiography showed decrease in ventricular systolic function, EF 27%
- Treatment: methylprednisolone, immunoglobulin, norepinephrine, diuretic, milrinone, piperacillin sublactam
- One week later, X-ray showed normal size of heart (F)

Echocardiography showed EF 66%

Management strategy of COVID-19 combined with CVD

- Induce COVID-19 infection
- Avoid acute cardiac events (heart failure, ACS)

Early self-management

Notice drug interactions

Diagnosis in time

Therapy for severe cases

- ECG, BP monitoring
- Early intervention
- Diagnosis of COVID-19 in time

- Respiratory support: rectifying hypoxia
- Circulation support: maintain volume balance
- Immunotherapy: Tocilizumab (TCZ)
Diagnosis and Treatment of Acute Myocardial Infarction and Protection of Cardiologists in COVID-19 outbreak

Shanghai Tenth People’s Hospital
Yi Zhang MD PhD FACC FESC
Yawei Xu MD PhD FACC FESC
General principles for AMI treatment

◆ Nearby treatment
Encourage AMI patients to seek and receive medical treatment at the nearest medical institution, minimizing patient transfer

◆ Safe protection
AMI patients with fever and other respiratory symptoms should have their first consultation at the fever clinic

◆ Thrombolysis first
In the case of suspected or confirmed COVID-19 infection, patients with STEMI should be admitted to an isolation room. Thrombolysis should be performed for those without contraindications

◆ Designated transfer
If the pathogenic test is positive for COVID-19, AMI patients with severe respiratory symptoms should be transferred to designated hospital

◆ Remote consultation
Encourage cardiologist to do remote medical consultations and guide the treatment of AMI in inferior hospitals
Flow chart of diagnosis and treatment for STEMI patients

1. STEMI patients with suspected or confirmed 2019-nCoV infection
   - Medical history, body temperature, electrocardiogram, chest CT scan, blood samples

2. Stable vital signs:
   - Yes
   - No

3. Unstable vital signs manifested with pneumonia:
   - Yes
   - No

4. STEMI onset > 12 h:
   - Yes
   - No

5. Contraindications for thrombolysis:
   - Yes
   - No

6. Thrombolysis in ICU:
   - Yes
   - No

7. Comprehensive evaluation of the benefits of PCI and the risks of infection control:
   - Yes
   - No

8. Benefits > risks?
   - Yes
   - No

9. Further treatment in ICU:
   - Yes
   - No

10. Selective PCI after the recovery of pneumonia:
    - Yes
    - No

11. Selective PCI:
    - Yes
    - No

12. Further treatment in isolation wards:
    - Yes
    - No
General principles

◆ House Quarantine: Avoid unnecessary hospitalization
For patients with stable cardiovascular disease, stay at home, avoid hospitalization

◆ Confirmed patients: Isolation in situ
For patients diagnosed as COVID-19 and severe cardiovascular disease, they should be isolated in situ, and the hospital administration should organize a cardiologist consultation to make a treatment plan

◆ Suspected patients: Designated hospital with designated operation room and ward
For patients with suspected COVID-19 and acute cardiovascular disease, they should be transferred to a designated hospital with designated catheterization lab

◆ Patients with fever: Consultation
For patients suffered from severe cardiovascular disease and fever, in-hospital expert consultation should be initiated with chest CT and routine blood test

◆ Intervention: Operation consent
For patients with suspected/confirmed COVID-19 infection requiring intervention/surgical treatment, the operation consent should be signed by a family member who has no history of close contact with him
Fever clinic was useful during SARS outbreak, and normally is set at the entrance. Patients with fever or respiratory syndrome are set for fever clinic, check routine blood test, assess contact and travel history, and chest CT scan.

If the cardiovascular disease has priority, remote consultant from cardiologists is recommended. Otherwise, cardiologists should be well protected with PPE.

If an urgent surgery or intervention is needed, cardiologists should report the case to the infection control department and medical affairs department.

If the patient is excluded for COVID-19, transfer them to the outpatients or emergency.