Stand on same side
Fight against COVID-19
Video conference between Europe and China
25th Mar.2020  15:00-17:00 (Beijing Time)  08:00-10:00 (Europe Central Time)

Prof. Alessandro Bartoloni

Director of the Infectious and Tropical Diseases Unit, Careggi University Hospital

Professor of Infectious Diseases, University of Florence
Prof. Alessandro Bartoloni

Covid-19 Update in Italy – Management in Careggi Hospital (Florence)

Our experience at Careggi Hospital with Covid-19 began on February 25th, 2020: at the moment (March 25th, 2020) we have treated 70 patients in the Infectious and Tropical Diseases Unit and 150 in total, we have 15 patients in intensive care and 24 in sub intensive care units.

We are treating patients with Lopinavir-Ritonavir, but if Kaletra is not compatible with other medicines or it is not tolerated, we administer the combination Darunavir / Cobicistat, other antiretroviral drugs; we also add hydroxychloroquine in the dosage of 200 mg twice a day.

At the moment we are not implementing any treatment for patients with mild symptoms: this is a point to discuss with you, as our strategy is to treat only moderate to severe cases.

However, we are evaluating whether to treat patients to prevent complications by involving primary care services. As a compassionate cure we are experimenting Remdesivir on 8 patients, 4 of whom are intubated, but at the moment we cannot use this treatment because we have not received these antiviral agents.

We joined the Italian study on Tocilizumab which is used in intensive care patients, intubated, in serious conditions; last week we started the treatment even in moderate cases.

We haven’t administered corticosteroids: we are discussing a lot about this and we would like to have suggestions also from your experience. We don’t use interferon.

We are planning to take convalescents’ plasma also here in Florence.

We are discussing about treatment strategies, as there are no clear results from clinical studies, antivirals, side effects: diarrhea, for example, is very common in our patients.

We would also like to be sure of hydroxychloroquine right dosage and to have more information about the combination of hydroxychloroquine and azithromycin, as a French group from Marseille recently found a synergy between the two medicines: this could be an oral treatment for non-hospitalized patients.

We are receiving several proposals about the use of immunomodulating drugs, but we lack solid data.

I take this opportunity to congratulate with the Chinese health system.

Adaptation and transcription: Dr. Giorgia Biagini
Revision: Prof. Lorenzo Corbetta
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Prof. Paolo Bonanni

Professor of Hygiene, University of Florence

Director of Specialization School in Hygiene and Preventive Medicine, University of Florence
Possible explanation of the high mortality rate in Italy (79.8% per million inhabitants) compared to other countries:

- The most advanced course of the epidemic compared to other EU countries.
- Population denominator on which the mortality rate is calculated (patients with a positive swab) - for example in China was it calculated on the basis of the whole nation or only the province of Hubei?
- Average age of patients with Covid-19 (51 years in China, most between 30-69 years, 20-29 years in South Korea, 63 years in Italy most between 80-89 years. Average age of deceased patients in Italy: 80 years, of which 48% of people with 3 or more diseases).
- Places available in intensive care and assisted breathing - health system’s stress.
- Diffusion in residences for the elderly.
- High average age of Italian population.
- Policy of use the PCR test for symptomatic cases only.
- Lowest mortality rate in Veneto, where multiple PCR tests are performed and the contacts are tracked.
Following Chart (March 24th, 2020) - Covid-19: numbers in Tuscany

Red points: number of cases
Pink Line: cases’ average of the last three days
Blue Line: peak’s forecast in Tuscany
Blue Line: cases’ number in Whan

The hope is that cases will start to drop in the coming weeks, although there are still many questions:

- We probably reached the peak of cases at the country level, but what about possible spread to southern regions?
- How long will we need to keep social distancing measures? At present every economic activity except for food, drug and chemical production and distribution is stopped
- Need to wait until how many cases in which geographic area?
- Need to put restrictions to travel from other countries in case of delayed epidemic peak outside the country

Adaptation and transcription: Dr. Giorgia Biagini
Revision: Prof. Lorenzo Corbetta
Covid-19 Update in Romania

We currently have approximately 800,000 cases (up to March 25, 2020) and 12 deaths in Romania. We are starting the quarantine, social distances started two weeks ago, while schools have been closing for three weeks; public spots (bars, restaurants, shops and so on) have been closing since last week. Romania is moving early, encouraging smart working too.

The national cases are 90% imported by people who have traveled outside the country, especially returning from Italy and Spain: the government has tried to isolate and quarantine these cases. Since last week the virus has also spread to people who did not return from abroad.

At the moment we only have tested about 300 symptomatic people per day, but we want to increase the number of tests especially in urban areas, where there is a greater concentration of people traveling for work.

From today people over 65-year-old cannot leave their homes, except for two hours a day and apparently they will be monitored by the police and the army.

This is the current situation in Romania. I must say that we are very lucky to learn from the experience of other countries and to implement the best practices.

Adaptation and transcription: Dr. Giorgia Biagini
Revision: Prof. Lorenzo Corbetta
**Clinical Diagnosis of Covid-19 and personal protection**

**Diagnosis**
The main Covid-19 route of transmission is via respiratory droplets and contact.
It is possible to spread by aerosol when exposed to high concentrations of aerosol for a long time in a relatively closed environment.
Covid-19 causes viral infection diseases, from simple infections (no complications), mild pneumonia, severe pneumonia, ARDS, sepsis, septic shock.
We can find inflammation and mucus in the lung, bronchoscopy helps us watching it.

**History of Epidemiology**
- Places where have been traveled: the epidemic area.
- Based on the current epidemiological investigation, the incubation period is 1-14 days, most of which are 3-7 days (14 days before onset is when you should pay close attention too).
- There is a contact history of Covid-19 patient (Nucleic acid testing positive).
- Clustering.

**Clinical Symptoms**
- With fever, dry cough, fatigue as the main performance. A few patients were accompanied by nasal congestion, runny nose, sore throat, myalgia and diarrhea.
In severe cases dyspnea and/or hypoxemia usually occur within one week of onset, and in severe cases they can rapidly progress to acute respiratory distress syndrome, septic shock, refractory metabolic acidosis, coagulation dysfunction and multi-organ failure.
- Some Children are relieved quickly.
- The mild patients only showed low fever, slight fatigue and no pneumonia sign.

Below you can see the Distribution of breath sounds in patients infected with Covid-19 (by electronic stethoscope devices).
We use electronic stethoscope because of the Personal Protection Equipment (PPE) we wear.

<table>
<thead>
<tr>
<th>Breath sounds</th>
<th>Anterior chest</th>
<th></th>
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<tbody>
<tr>
<td></td>
<td>Left upper</td>
<td>Right upper</td>
<td>Left middle</td>
<td>Right middle</td>
<td>Left basal</td>
<td>Right basal</td>
<td>Left upper</td>
<td>Right upper</td>
<td>Left middle</td>
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<tr>
<td>Normal</td>
<td>33 (57.9)</td>
<td>31 (55.4)</td>
<td>22 (38.6)</td>
<td>23 (40.4)</td>
<td>12 (21)</td>
<td>13 (24.1)</td>
<td>23 (40.4)</td>
<td>29 (51.8)</td>
<td>14 (24.6)</td>
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<tr>
<td>Coarse breath sound</td>
<td>15 (25.3)</td>
<td>14 (25)</td>
<td>17 (29.8)</td>
<td>17 (29.8)</td>
<td>19 (33.3)</td>
<td>11 (20.4)</td>
<td>14 (24.6)</td>
<td>10 (17.9)</td>
<td>18 (31.6)</td>
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<tr>
<td>Tubular breath sound</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>1 (1.8)</td>
<td>0 (0)</td>
<td>0 (0)</td>
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<td>0 (0)</td>
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<tr>
<td>Wheezes</td>
<td>2 (3.5)</td>
<td>4 (7.1)</td>
<td>1 (1.8)</td>
<td>2 (3.5)</td>
<td>1 (1.8)</td>
<td>2 (3.7)</td>
<td>4 (7)</td>
<td>5 (8.9)</td>
<td>3 (5.3)</td>
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<tr>
<td>Medium-coarse crackles</td>
<td>2 (3.5)</td>
<td>3 (5.3)</td>
<td>7 (12.3)</td>
<td>6 (10.5)</td>
<td>9 (15.8)</td>
<td>13 (24.1)</td>
<td>4 (7)</td>
<td>5 (8.9)</td>
<td>11 (19.3)</td>
</tr>
<tr>
<td>Fine crackles</td>
<td>4 (7)</td>
<td>3 (5.6)</td>
<td>8 (14)</td>
<td>5 (8.8)</td>
<td>10 (17.5)</td>
<td>12 (22.2)</td>
<td>10 (17.5)</td>
<td>5 (8.9)</td>
<td>5 (8.8)</td>
</tr>
<tr>
<td>Voice crackles</td>
<td>1 (1.8)</td>
<td>2 (3.6)</td>
<td>2 (3.5)</td>
<td>4 (7)</td>
<td>5 (8.8)</td>
<td>1 (1.8)</td>
<td>3 (5.3)</td>
<td>1 (1.8)</td>
<td>8 (14)</td>
</tr>
<tr>
<td>Pleural friction rub</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
</tbody>
</table>

In reference to the Laboratory testing, the Blood Routine Examination shows that the total number of peripheral blood leukocytes in the early stage of the disease was normal or decreased and the lymphocyte count was decreased.
CRP and erythrocyte sedimentation rate were increased in most patients and procalcitonin was normal. In severe cases, D-dimer increased, and peripheral blood lymphocytes decreased progressively.
**Virus Detection**

**The specimen**
- Throat swab/nasopharyngeal swab/anal swab;
- Specimens of sputum and other secretions of the lower respiratory tract, faces etc. Detection of lower respiratory tract, faces, etc. Detection of lower respiratory tract specimens (sputum or airway extract) is more accurate.
- 4 hours after the sample collection for test (4 degrees for 24 hours / -70 degrees for longer preservation).

**Testing methods**
- RT-PCR
- NGS

The nasal swab is more accurate than the pharyngeal swab, that’s why we use it to detect the virus.

**Immunological Test**

Covid-19 specific IgM antibody usually appears positive after 3-5 days of the disease’s onset. The titer of Ig antibody in the recovery stage was 4 times higher than that in the acute stage.

**42 year-old woman case**

With the CT scan we observed multiple small patches and interstitial changes in the early stage. Most of the changes are located at the lung periphery. Then, it developed into multiple ground-glass opacity, lung consolidation gradually appeared. During the recovery period the ground glass opacity appeared again, subpleural line (pleural effusion is rare).
For a complete diagnosis I suggest to use together Clinical + Laboratory Testing + Imaging.

We use three types of classification for the virus: Mild, Common Type, Severe:

I. **Mild** mild clinical symptoms, no evidence of pneumonia on imaging
II. **Common type** have fever, respiratory tract and other symptoms, imaging can be seen pneumonia.
III. **Severe (adult meets any of the following criteria)**
   - Shortness of breath, RR30 times/min;
   - At rest, oxygen saturation ≤93%;
   - Arterial partial oxygen pressure (PaO2)/oxygen absorption concentration (FiO2) ≤300mmHg (1mmHg = 0.133kPa).
   - Correction of PaO2/FiO2 at high altitudes (over 1000 m) shall be made according to the following formula: PaO2/FiO2 * [atmospheric pressure (mmHg)] / 760.
   - Pulmonary imaging of patient, showing significant progression greater than 50% of lesions within 24-48 hours

IV. **Critical type (one of the following)**
   - Respiratory failure and need mechanical ventilation;
   - Shock;
   - Combined with other organ failure and requires ICU care.
Clinical warning index of adult severe and critical type
- Peripheral blood lymphocytes progressively decreased.
- Peripheral inflammatory factors such as IL-6 and CRP increased progressively.
- Lactic acid is progressively elevated.
- Lesions on CT progress rapidly in a short period of time.

Risk Factors for progression to severe and critical disease
- Age
- Obesity
- COPD
- IPF
- CTD-ILD
- Chronic heavy smoking
- Basic cardiovascular disease such as hypertension
- Basic disease of nervous system such as cerebral infarction
- Chronic kidney disease

We have to pay attention because we don’t know enough about the new Coronavirus:
- Clinical symptom is apparent, nucleic acid is negative
- CT change is obvious, nucleic acid negative
- No clinical symptoms, nucleic acid positive
- Cynical symptoms disappeared, nucleic acid positive
- CT lesion completely absorbed, nucleic acid positive

Moreover we need to proceed with a differential diagnosis from the other disease such as influenzavirus, adenovirus, respiratory syncytial virus etc.

Personal Protection – Quarantine measures
- Respiratory droplets isolation
- Contact Isolation
- Aerosol Isolation

Personal Protection – Personal Protective Equipment
**Standard protection (primary protection)**
- Wear disposable work cap, disposable surgical mask and work cloths (white coat) and disposable latex gloves if necessary.
- Applicable to general diagnosis and treatment activities: pre-check triage, general outpatient, outpatient department of infection.

**Enhanced protection (secondary protection)**
- Wear disposable working cap, protective glasses (anti-fog type)/face shield, medical respirator (N95), protective clothing or work clothes (white lab coat), disposable protective clothing and disposable latex gloves, disposable shoe cover when necessary.
- It is applicable to the medical staff in close contact with patients in the diagnosis and treatment activities.

**Additional protection (tertiary protection)**
- Wear disposable working cap, full respirator or positive pressure head cover, medical respirator (N95), protective clothing or work clothes (whitecoat), disposable protective clothing, disposable latex gloves and/or disposable shoe cover.
- It is applicable to perform sputum aspiration, respiratory tract sampling, bronchoscopy, intubation and tracheotomy.

**How to wear PPE**

![Image of PPE wear method]

*Use protective equipment correctly*
1. Wear work cap
2. Wear medical protective mask
3. Test for tightness
4. Check protective clothing
5. Wear protective clothing
6. Wear inner gloves
7. Wear outer protective clothing
8. Wear outer gloves
9. Wear protective mask
10. Wear waterproof boot cover
11. Wear outer shoe cover
12. Check wearing

*Appearance after wearing*
Hand Hygiene
- Medical institutions should set up facilities for washing hands with running water and sanitizing hands.
- For medical institutions with adequate financial support, non-contact faucet should be equipped in the area of diagnosis and treatment and to be equipped with hand warmer or one-time use wipe hand towel too.

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Prof. Felix JF Herth
Prof. Dr. med., Dipl. Oec.med.
医学博士，医药工商管理学硕士
CEO and CMD of Thoraxklinik am Universitätsklinikum Heidelberg
海德堡大学附属胸科医院执行院长及首席院长
Head, Department of Internal Medicine, Pulmonology and Critical Care
呼吸内科及危重症部门主任
Secretary of the European Association for Bronchoendoscopy and Interventional Pulmonology (EAB)
欧洲支气管镜和介入性肺脏病学会秘书
This is the updated list of European countries where Covid-19 has spread (as of March 25, 2020), Italy is undoubtedly the most affected, Germany ranks third with almost 30,000 cases.

It seems that the plateau was reached on 21/03, but we don't know if it really is, or we still have to get there.
As for the virus’ geographical distribution, the red area defines where the largest number of patients with Covid-19 is located. Other areas have been attacked more, those bordering France, Austria where the Germans went skiing above all due to the coronavirus outbreak in Tyrol - particularly in Ischgl, but also in the central area where the carnival was held.

According to these data, Germany is currently in a less worrying situation than other European countries:

- **82,8 Million Germans**
- **33416 ill patients (Probability of illness 0,04 %)**
- **156 patients died (Mortality 0,5 %)**

**Testing Strategy**
In Germany tests are made if at least one of the following two conditions occurs:
- Acute Respiratory Symptoms of any severity or a-specific general symptoms;
  AND - having been in contact with a confirmed or probable case of Covid-19 in the last 14 days before the symptoms’ onset;
OR - having traveled / resided in a Covid-19 transmission area for the last 14 days before the symptoms’ onset.
Current situation in the area of Prof. Herth, Heidelberg
- Around 300 tests per day;
- of which 407 positive in total (66 hospitalized of which 9 in ICU).

With reference to the therapies, as already explained by Prof. Zhong, we are carrying out treatments with Chloroquine and Kaletra, we hope that everything goes in the right direction.

Germany has adopted preventive lockdown measures following the example of the China: schools are closed, social activities limited to the maximum level to avoid an uncontrolled virus’ spread and to overshadow hospital capacity.

In summary in Germany we are following this line: Preparation and Prevention.

Adaptation and transcription: Dr. Giorgia Biagini
Revision: Prof. Lorenzo Corbetta
Prof. Shiyue Li

Bronchoscopy in Covid-19 patients

Focus on these topics:
- General Practice in Bronchoscopy;
- Diagnosis
- Treatment
- Summary

At the beginning of March the following Expert Consensus was published, it is focused on the following points:

- Conducting bronchoscopy on patients with 2019-nCoV is a high-risk procedure in which health care workers are directly exposed to the virus
- The indications for bronchoscopy for other diseases should be strictly mastered
- Bronchoscopy should not be used as a routine means for the diagnosis of 2019-nCoV infection sampling.
- the Personal Protective Equipment (PPE) is required

I would like to talk about my hospital’s experience by analyzing tracheal intubation on 12 patients with Covid-19
In some cases of Covid-19 it seems to be mucosa hyperemia, swelling, a small amount of secretions:

Smooth bronchial mucosa, clear lumen and little secretions are more common
In the table below, part of the article "Evaluating the accuracy of different respiratory specimens in the laboratory diagnosis and monitoring the viral shedding of 2019-nCov Infections", Yang Y, Yang M, Chen C et al., we see how the BALF value increases a lot from the eighth to the fourteenth day after the disease’s onset. Therefore it is appropriate to focus on this value.

I analyze another case of my hospital:
- Male 49 years
- 2 weeks after the onset
- Mechanical ventilation with high airway resistance, hypercapnia
- OCT (Optical Coherence Tomography)

We can see:
Difference in the Lumen diameter, area, wall area and AW percentage
Progressions of the Lumen:

```
Aw% = \frac{AW}{AW+AW} \times 100%
```
Findings:
- No significant decrease in the Lumen area of 3-9 grade bronchi, which is similar to a person without Covid-19.
- The bronchi wall of grade 3-9 is slightly thicker than in a normal person with mild mucosa edema.
- Mucos retention occur the most in 4-6 grade bronchi.

Bronchoscopy Treatment:
- Clear away airway’s secretion;
- BAL.

Example of Bronchoscopy Treatment:
I show you the equipment we are using, very efficient:

Summary
- Bronchoscopy in Covid-19 patients is a high risk procedure;
- The Personal Protective Equipment (PPE) is required during the procedure;
- In some cases bronchoscopy has unique advantages.

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Prof. Jonathan Van-Tam

Deputy Chief Medical Officer at Department of Health and Social Care, England
Professor of Health Protection, Clinical Professor
University of Nottingham
Covid-19 Update in UK

The first UK policy to contain the Covid-19 epidemic was to identify cases from abroad, from the areas already affected, for a period of time (although there was no control group that indicated the efficiency of the strategy). We reached a point of no return when the cases in Italy and Iran, countries with which we have strong connections, started to grow rapidly, as we were unable to close indirect routes to the United Kingdom; also British citizens were returning from these areas. This has led to a rapid cases’ increase: in the last ten days we have started to adopt restrictive social distance rules up to 48 hours ago (as of March 25th, 2020), when the following points were decided:
- if there is a domestic Covid-19 case, all tenants must be quarantined for 14 days;
- further social distance rules, leaving open only stores that sell necessity goods;
- smart working where possible;
- citizens can exercise outdoor for a while a day, keeping a distance of at least two meters from people who are not part of the same family;
- citizens can go out to buy necessity goods (as few times as possible), buy medicine;
- citizens can go out to take care of a single person in total self-isolation.

For patients with comorbidities or immunosuppressed patients we have introduced a policy called "Shielding": they won’t have to go out for three months from home (they can still go out to buy food). They will be supported by the authorities, or by friends and neighbors.

In terms of the ICU surveillance system, the cases are continuing to grow, the patients we are witnessing have contracted the virus at least 10-14 days before the disease begins, so we do not expect to see positive turns in the ICU hospitalization curve at least for the next two weeks.

UK Health System

We are proceeding like Germany in terms of prevention and preparation not to have problems with the capacity of hospital beds.
It was already a plan of British Health System to double the intensive care unit’s capacity, now an entire Conference Center in London will become an hospital with 4000 new beds in a short time, approximately in a week. We are preparing for the next two weeks, when cases increase further, after which we hope that the curve will start to go down.

Clinical Trials

Clinical trials are underway in 138 facilities in the UK with Keleta, Chloroquine, Support Therapy, Dexamethasone.

We have the intention to understand if we can reduce the hospitalization of patients by immediately treating them with Hydroxychloroquine and Supportive Therapy: approximately in seven days we begin to recruit high-risk people (>50 years or >65 years that may also present comorbidities) who have Covid-19 compatible symptoms.

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Prof. Nanshan Zhong 钟南山院士

Academician of Chinese Academy of Engineering, respiratory expert
中国工程院院士, 著名呼吸病学专家

Director of the National Clinical Research Center for Respiratory Disease
国家呼吸疾病临床医学研究中心主任

Head of the Senior Expert Group of the National Health Commission
国家卫建委高级别专家组组长
Strategy for anti-Covid-19 in China

We are talking about a pandemic that has caused so far (25/3/2020) 422,550 cases and 18,779 deaths (4.4%) worldwide in 195 countries.

In addition to the transmission’s characteristics (contact, exchange of fluids, contamination, air transport - transmission from mother to child and through feces to be verified), I would like to focus on asymptomatic patients, however they are virus’s carriers, and indeed, highly contagious.


It’s analyzed the case of an asymptomatic index patient who resides in Shanghai and who participates in a meeting in Germany from 19 to 22 January; only once he returns back to China he has started to experience the symptoms. Probably when the patient left for Germany he already was suffering from Covid-19, but asymptomatic, infecting two participants at the meeting.

What I mean is that the Basic Reproductive Number, according to published reports, is approximately 3.0, higher than Sars (2.0-3.0), Mers (<1.0) and, obviously seasonal influence (1.5), and that a big problem is represented by the fact that the virus mainly involves the upper airways in the initial phase of the onset, and then significantly decreases a week later.

Therefore, we must pay attention to the following delicate points:
- A high Basic Reproductive Number (RO), approx 3
- A high mortality compared to the flu (0.7% -7%, approx 4%)
- Human transmission due to asymptomatic carriers and this is why we fear the new cases very much
- Transmission is greater in the disease onset initial’s phase
- Important not to block sewers and drain pipes.

Diagnosis in China
- Diagnosis of Covid-19 infection in suspicious people: initially we made the PCR swab, now we prefer to perform a double check, that is Real Time PCR (Virus RNA) and POCT for IGM
- Differential diagnosis between covid-19 and Influenza (A, B)
The IgM appears in the initial phase: approximately in the 7 or 8 days following the infection or 4 days after
the disease’s onset. Therefore we have to make differential diagnoses between Covid-19 infection and Influenza, that’s
how we are proceeding in China, quite difficult from a clinical point of view.

Clinical features
This Data were collected by Prof. Zhong’s medical team in Wuhan at the very beginning:

The average number of the virus incubation’s days are 4, in a period of time ranging from 2 to 7 days.
Another point that I want to emphasize is the fact that cough and fever are the most common factors of Covid-19,
but more than 50% of the patients in our group were afebrile at the time of admission, so the fever mustn’t be
considered a Gold Standard.

More than 85% of patients at the time of hospitalization have thoracic CT with abnormalities, very commonly with
lung nodules and bilateral infiltrations, in particular distributed in the sub pleural area.
Laboratory results show lymphopenia and commonly elevated levels of CRP, LDH and direct bilirubin.

We have carried out an important study and created a tool to predict Covid-19 critical illness thanks to the analysis of answers to the following questions about risk's factors: X ray abnormality, age, hemoptysis, dyspnea, state of consciousness, comorbidities’ number, cancer history, NLR, lactate dehydrogenase, direct bilirubin (Liang W. et all, under review)

Calculation Tool’s Internet address is http://118.126.104.170/

**Therapy and clinical trials**
Clinical studies are underway on:
- Lopinavir-Ritonavir (Kaletra)
- Chloroquine
- IL-6 receptor antibody (tocilimab)
- LHQW capsule (medicine made from Chinese herbs)
- Hydrogen-Oxygen gas inhalation
- Convalescence plasma
- Remdesivir

We have some results to share:
The first Covid-19’s national clinical trial is about the administration of Lopinavir-Ritonavir based on the primary endpoint, showing no significant efficacy.
The second study, in presentation and publication phase, is about the treatment with Chloroquine:

Below we see the parameters on which the study is based:

**Clinical application of chloroquine**

- **Enrollment:** 156 participants from 10 designated hospital until 20th Feb
- **Treatment:** subjects take chloroquine 0.5g/day bid for 10 days
- **Preliminary data:** throat swabs in 103 of 120 participants turned negative
- **Adverse reaction:** generally well tolerated

**Plasma concentration**

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<tr>
<th>Case</th>
<th>Withdrawal days (d)</th>
<th>1</th>
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<th>3</th>
<th>4</th>
<th>6</th>
<th>7</th>
<th>8</th>
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<td>1</td>
<td>0</td>
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**Blood concentration (μmol/L)**

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<th></th>
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<th>1.24</th>
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<th>0.85</th>
<th>0.62</th>
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<th>0.19</th>
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</thead>
</table>

**EC50 chloroquine against SARS-CoV-2 close to blood concentration**

- **EC50:** 1.13μmol/L
- **Blood concentration:** 1.54μmol/L (D1 withdrawal) 1.24 (D1 withdrawal)
- **No chloroquine accumulation according to dynamic monitoring**

Nanshan Zhong, Shansheng Jiang, Zifeng Yang, et al. unpublished data
The study results are good in terms of efficacy and safety of Chloroquine treatment:

- Patients in the chloroquine group have a **shorten time** to reach undetectable viral RNA comparing with the control group (median, 3 d vs. 9 d; \( P < 0.001 \))
- By day 10 and day 14, **higher proportion** of patients had viral RNA turning to negative (chloroquine group: 91.4%, 95.9%), as compared to the control group (57.4%, 79.6%).
- Duration of **fever significantly shorter** in chloroquine versus control group (\( P = 0.003 \))

Unpublished data

TMCs and other antiviral drugs show inhibitory effects against Covid-19 in vitro.

<table>
<thead>
<tr>
<th>Drugs</th>
<th>TC50 (μg/mL)</th>
<th>EC50 (μg/mL)</th>
<th>SI</th>
</tr>
</thead>
<tbody>
<tr>
<td>LHQW</td>
<td>1197.75</td>
<td>414.02</td>
<td>2.89</td>
</tr>
<tr>
<td>LS</td>
<td>2.706</td>
<td>0.76</td>
<td>3.64</td>
</tr>
<tr>
<td>RDN</td>
<td>104.8</td>
<td>18.24</td>
<td>5.70</td>
</tr>
<tr>
<td>JZ</td>
<td>29.44</td>
<td>5.85</td>
<td>5.03</td>
</tr>
<tr>
<td>HQ</td>
<td>&gt;1000</td>
<td>231.47</td>
<td>&gt;4.32</td>
</tr>
<tr>
<td>Arbidol</td>
<td>44.72</td>
<td>10.715</td>
<td>4.17</td>
</tr>
<tr>
<td>chloroquine</td>
<td>&gt;85.4</td>
<td>1.13</td>
<td>&gt;75.6</td>
</tr>
<tr>
<td>Remdesivir</td>
<td>&gt;100</td>
<td>0.825</td>
<td>&gt;121.21</td>
</tr>
</tbody>
</table>

The LHQW capsule study also shows some positive results.
There is no significant difference in the conversion rate in severe cases or viral conversion time between the groups.
Convalescent plasma - Pilot study on the use of convalescent plasma (print phase). The study’s parameters are the following:

**The feasibility of convalescent plasma therapy in severe COVID-19 patients: a pilot study**

Kai Duan1,2, Bende Liu3, Cesheng Li4, Huajun Zhang5, Ting Yu6, Jieming Qu7, Min Zhou8, Li Chen9, Shengli Meng2, Yong Hu3, Cheng Peng9, Mingchao Yuan9, Jinyan Huang9, Zaijun Wang10, Jianhong Yu6, Xiaoliao Gao5, Dan Wang3, Xiaoxu Yu1, Li Li7, Jiayou Zhang1, Xiao Wu4, Bei Li5, Yanping Xu2, Wei Chen1, Yan Peng9, Yeqin Hu9, Lianzhen Lin5, Xuefei Liu1, Shihe Huang1, Zhijun medRxiv preprint doi: https://doi.org/10.1101/2020.03.16.20036145.

- Recovered donors with the neutralizing antibody titers above 1:640
- N=10, one dose of 200 mL convalescent plasma (CP)
- Primary endpoint: safety of CP transfusion.
- Second endpoints: improvement of clinical symptoms and laboratory parameters within 3 days after CP transfusion

The results show an improvement, in most cases a decrease of values, of clinical factors apart from the total bilirubin.

| Table 3. Comparison of laboratory parameters before and after convalescent plasma transfusion |
|----------------------------------------|-------------------------------|-----------------------------------------|
| Clinical Factors                      | Before CP transfusion         | After CP transfusion                    |
| C-reactive protein (mg/L, normal range 0-6) | 55.98 (15.57-66.67)            | 18.13 (10.92-71.44)                     |
| Lymphocyte (10^9 per L, normal range 1.1-3.2) | 0.65 (0.53-0.90)             | 0.76 (0.52-1.43)                        |
| Alanine aminotransferase (U/L, normal range 9-50) | 42.00 (28.25-61.85)          | 34.30 (25.75-53.90)                     |
| Aspartate aminotransferase (U/L, normal range 15-40) | 38.10 (28.50-44.00)         | 30.30 (17.30-38.10)                     |
| Total bilirubin (μmol/L, normal range 0-26) | 12.40 (11.71-22.05)          | 13.98 (12.20-20.80)                     |
| SaO2 (%) (normal range ≥95) | 93.00 (89.00-96.50)          | 96.00 (95.00-96.50)                     |

The serum neutralizing antibody titers’ values show an increase after the therapy and the SARS-Cov-2 RNA load is negative.

**China’s strategy to control the spread of the virus**

January 20th: the spread from man to man is defined and announced. It comes the confirmation that some medical personnel has been infected.

On January 23, after just 3 days, Whuan’s lockdown is announced: "Don't go to Whuan, Don't leave Whuan". National announcements are made in real time about the number of patients, suspected ones. Containment and early protection measures, early diagnosis and early isolation are activated in every city of the nation.
Thanks to these measures we reached the peak in two weeks, on February 4th; after four weeks we are under control.

Important consideration about the lockdown’s interventions and restrictive social measures in general: if we had intervened in China 5 days later, the number of infected would have almost tripled.
Currently in Europe the curve of infected patients deriving from positive swabs is growing:

Conclusions: since the infected patients (deriving from positive swabs) is still growing in Europe, I recommend the lockdown and other restrictive measures such as self-protection, self-isolation, but also early diagnosis.

Adaptation and transcription: Dr. Giorgia Biagini
Revision: Prof. Lorenzo Corbetta
Discussion Questions

- Problem of health workers. In Italy, especially in Lombardy, there are many infected doctors (10%). In the USA, Ohio, 60% is infected. How did you solve or face the problem? How can we protect doctors from infection, must we prevent everyone from arriving in the hospital?

  Prof. Zhong: At the very beginning in Wuhan many doctors were infected, because there was no protective equipment, I think the reason is the same for Italy. In addition, the medical staff worked without rest, in a month we had been organizing ourselves so that the working conditions were sustainable and with adequate protective equipment, to be appropriately worn. Since we have taken these measures, only a few doctors have become infected, as far as I know two or three.

- Especially in Lombardy several doctors treating hospitalized patients and have been infected, consequently their families, starting the chain of infection.

  Prof. Zhong: The problem in Italy, as in many other countries at the beginning of the pandemic, was to focus only on symptomatic patients without giving the due importance to cross-infection (family, relatives, colleagues, etc.), very important for the path's transmission. During incubation, people are highly contagious, whether they have symptoms or not. Social occasions facilitate the virus transmission. I also believe that the high mortality rate of elderly people in Italy (average age 80 years) is normal to the extent that they are immunosuppressed subjects. In mid-January I met infected medical personnel in Wuhan who were not working in the infectious disease unit, unaware about the infectivity rate. The first part of the infection started from the neurological department, where 13 doctors were infected by a patient: in Italy, as in every other part of the world, people must be aware of the fact that protections from the virus must be adopted in each hospital unit.

- Can we create a prophylaxis for medical personnel by administering medicines such as chloroquine?

  Prof. Zhong: There is no evidence that chloroquine or hydroxychloroquine prevents infection. In response to Prof. Bartoloni regarding the dosage of hydroxychloroquine for 200 mg twice a day, we administer 500 mg twice a day for 10 days on more than 20 patients. Our follow up showed a blood concentration of 1.6 micromoles, which is enough to kill the virus, far from being toxic anyway. The toxic window according to NEJM is 20 micromoles. I suppose the Massachusetts General Hospital guidelines about the administration of hydroxychloroquine, related to some in vitro studies, recommend 400 mg twice a day for four days, then 400 mg once a day for five days. However, I believe currently there isn’t a controlled drug study.

- Cases of death from uncontrolled viraemia and cytokine storm. Can we think of a personalized treatment?

  Prof. Zhong: In some patients with several negative PCRs, when we underwent a lung transplant, we still found some virus in the lungs. Most of the advanced patients are however affected by viraemia, I suppose the damage to the organs is caused directly by the virus: we must focus on antivirals and anti-inflammatories.

- Are there sequelae after months in the lungs (fibrosis, impaired lung function) in patients with pneumonia?

  Prof. Zhong: It is not like SARS, in patients that are hospitalized for a long time, for example a month and a half with ventilation, the fibrosis is reversible, I am not worried about the functionality of the lungs.

- How to prevent the second wave of the virus

  Prof. Zhong: I think it is better to focus on people from abroad, on importing the virus. To block traffic routes or otherwise to have special attention even for those people who haven’t symptoms by double-checking after one week.
Prediction for India

Prof. Zhong: The climate is mild, the virus should spread with more difficulty, anyway I know that social distance measures have already been taken.

Prediction for Italy

Prof. Zhong: I think it will get better in Italy in the near future. There has been a huge increase in cases from 1 to 20 March and the country is heading towards the peak, which should be within a week and then start to go down. From the beginning of the infection, the forecasts before a descent is 3-4 weeks.

In China we had an increase of two weeks only thanks to strict restrictions; if Italy continues with this restrictive legislative line, although it cannot predict it exactly, there should be no problems.

- Duration of immunity, possibility of relapse

Prof. Zhong: The IGM is seen three days after the infection and then rises and lasts other 7 days, after which it drops. The IGG grows for a week and then for another week.

The course of the disease is estimated to be approximately two weeks (also for mild symptoms and patients without treatment).

- Are the antibodies protected by a second attack?

Prof. Zhong: Yes, they are higher, more or less four times. I have not seen any double-infected patient.

At the moment I believe that the only effective treatment is convalescent plasma.