

INTERVIEW

COVID-19 management: **patient pathway, from diagnostic to treatments (current and in development)**



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1 What are the numbers of diagnosed-COVID-19 patients in France, Europe, worldwide? How many of them displayed severe symptoms requiring hospitalization in Intensive Care Unit?

Pr X. Lescure:

- France: around 165,000 cases have been confirmed COVID to date, with important differences between areas, most of patients having been identified in the East of France, the North of France and around Paris. But modelling approaches and the first seroprevalence studies estimate the real number of COVID infections in France around 3 million /4.4 % of the general population. The epidemic in France is currently controlled in the metropole with still some clusters identified and tracked but today, Guyana and Mayotte are doing front to an epidemic phase.
- In Europe: as of July 5th, 2020, 1,549,904 cases have been reported in the EU/EEA and the UK. The most largely impacted countries are: United Kingdom (284,900), Spain (250,545), Italy (241,419), Germany (196,335), etc.
- As of July 5th, 2020, 11,449,000 cases have been reported all around the world. The most impacted countries are the United states with more than 2,880,000 cases, Brazil with more than 1,600,000 cases, Russia and India with more than 650,000 cases. All these countries still present a current epidemic phase.

Around 5-7% of patients have severe presentation needing critical care in ICU. Mortality rate depends mainly to the denominator /the capability to identify all the cases, the saturation or not of the health care system and the characteristics of the population regarding the risk factors such as mean age, proportion of obesity and other burdening comorbidities.

- **Pre-symptomatic phase:** persons with positive SARS-CoV-2 PCR before onset of COVID symptoms, this is a transitory status. Persons considered to be asymptomatic could become symptomatic and have to be called actually pre-symptomatic. Studies have shown that patients had positive SARS-CoV-2 PCR 2 days before presenting the onset of the disease. It is another difficulty for controlling the circulation of the virus.
- **Mild form:** flu like syndrome such as fever, cough, intense fatigue, myalgia/athralgia, pharyngalgia, headache, chill, but also nausea/vomiting or diarrhea. Without any severity criteria, these patients can be managed in the primary care system with symptomatic treatment. According to risk factors for severity such as age, male gender, chronic disease (cardiac, pulmonary, kidney, neurological disorders), obesity, dementia, malignancy, liver disease; patients could have a theoretical benefit to receive a specific treatment to prevent worsening. Studies in the community are going on.
- **Severe form:** mainly shortness of breath occurring around 20% of symptomatic cases. These patients have to be monitored in hospital and can need oxygen therapy. Probably according to inflammation parameters, corticosteroids present a benefit on survival. These patients should receive an antiviral treatment but today, (hydroxy)chloroquine and lopinavir/ritonavir failed and remdesivir would present a limit positive impact on duration of the disease (preliminary analysis).
- **Critical form:** Acute Respiratory Distress Syndrome with two different kind of presentations. A « low elastance » ARDS with gas volume nearly normal, low recruitability and loss of hypoxic pulmonary vasoconstriction (ground glass densities). A high elastance with increase oedema and decrease gas volume and high recruitability (bilateral condensations).

On a radiological point of view, CT scan is more sensitive than X-ray. We can see ground glass densities at the beginning which can progress to bilateral condensations. To characterize severity with CT scan, specialists proposed a scale: <10%, 10-25%, 25-50% and more than 50%.

The chronogram of the natural history of COVID is 7 days from onset of symptoms to first hospital admission, 8 days from illness onset to dyspnoea, 9 days to ARDS and 10 days to ICU admission.

2 Can you explain the main COVID-19 patient profiles and their management?

Pr X. Lescure:

- **Asymptomatic status:** persons with positive SARS-CoV-2 PCR without any symptoms. The proportion of asymptomatic patients is not rare; around 20 and 30 % according to the studies. This is a reassuring signal at a clinical point of view for the pathogenicity of the virus, but it represents a complexity factor on an epidemiological point of view in order to tackle the circulation of the virus. Even if the absence of symptoms could lead persons to be less transmitters.

3 In your hospital, what were/ are the main complications that you have treated and how did you detect them? Do you think that you could see unknown complications in the coming months?

Pr X. Lescure:

- Cytokinic storm – ARDS; lung damage and multi-organ damage, detected by oxygen requiring, inflammatory syndrome (C-Reactive Protein is enough, Interleukine-6 was not dosed in our hospital), bilateral condensations at CT scan.

- Cardiovascular diseases; acute myocarditis, acute myocardial infarction, acute heart failure, dysrhythmias and pulmonary embolism. Electrocardiogram and echocardiogram were systematic in our hospital and angio-CT (contrast-enhanced) scan was performed as soon as the least suspicion was evoked. Antithromboembolic prophylactic treatment was systematically prescribed for hospitalized patients, dosing varying according to the weight and the risk factors. The D-dimers with a cut-off of 1000 was used.
- Renal failure: multifactorial with predisposing factors. Implementation of Kidney Disease Improving Global Outcome guidelines restoring normal volume status and reducing the risk of pulmonary oedema, right ventricular overload, congestion
- Cognitive impairment: difficult to assess precisely. Patients had sometimes a non-adapted behavior without any clearly signs of encephalitis. First patients had CNS explorations without finding meningo-encephalitis or cerebro-vasculitis.
- Post traumatism stress: the pandemic context and the absence of effective specific treatment have induced important anxious troubles.

I do not think that we could see unknown complications in the coming months for the acute phase because we have managed a lot of patients and we have shared a lot of experience with colleagues from other centers in France and outside of France. But I think that we do not know exactly the post-infectious COVID with some complicated signals for the moment.

4 Which type of therapies (vaccines, anti-viral, anti-cytokines,...) are currently used and are under development? Which ones are at the most advanced stage? Which countries lead the development of the new therapies?

Pr X. Lescure:

- Available antivirals: at Bichat hospital, we used lopinavir/ritonavir (anti-viral therapies) in first line, remdesivir (anti-viral therapy) or hydroxychloroquine (anti-viral therapy) if contra-indication or interactions. Today, we know that neither lopinavir /ritonavir nor hydroxychloroquine work. Studies about remdesivir shown a limited positive impact on duration of the disease but not yet on the mortality. Data have to be confirmed.
- Anti-cytokines or immunomodulators: in our hospital, we used the systemic corticosteroids when patients required oxygen therapy more than 3l/min and presented a biological inflammatory syndrome (CRP more than 40 mg/L). In case of non-response to corticosteroids, we used anti-cytokines such as anti-Interleukine-1. Since this time, a Randomized Controlled Trial shown that corticosteroids were associated with a significant

improvement of the mortality. Data are under process of publication. Prospective and interventional analyses about anti-cytokines are going on.

- Convalescent plasma seems to represent a hope from first observational data, RCTs are going on. We did not use this treatment during the first wave because of the heavy constrains of these treatment modalities.
- Vaccines. There are 8 types of vaccines: virus (inactivated, weakened), viral vector (replicating, non-replicating), nucleic acid (DNA, RNA) and protein based (protein subunit, virus-like particles). More than 100 candidates in preclinical development are listed, 13 candidate vaccines in clinical evaluation. This is the Graal but the route is still long.
- To date, the UK has a leader position for the development of the new therapies, especially because authorities succeeded in the very difficult task to coordinate the clinical research with a big adaptive clinical trial.

5 What were/are the main organizational (direct and indirect) impacts in your hospital for COVID-19 and non-COVID-19 patients?

Pr X. Lescure:

- COVID: from 7 emerging and biological risk beds to all the ID departments (59 beds), 260 COVID beds in Bichat hospital at the peak of the epidemic, including 70 ICU beds with a large extension of the critical care in the post-anesthesia and surgery rooms. A dedicated pathway from Emergency Department to ICU including radiology and gerontology. Procedures quasi "military designed" for optimizing the management and well integrating non specialist and/or external reinforcing staff. Pneumologists, rheumatologists were involved in the management when ID department was full. A digital solution was created and implemented for following non severe patients at home with a daily auto-questionnaire and an automatic alert to a command medical center. Nearly 60,000 patients have been enrolled in this application.
- Non-COVID: de-programming for chronic diseases or non-urgent surgery, entire units were closed to move manpower in COVID units, outpatients' activities were boosted, tele- or visio-consultations were also developed.

6 How did you get/are getting prepared to the different scenarios for the upcoming 6 months?

Pr X. Lescure:

I think that the risk of resurgence of COVID-19 is particularly important. It can occur during the summer or the autumn according to the sensitivity of the virus to the temperature (relative), and the behavior of people. It can be integrated among the other virus of community respiratory infections or lead to another epidemic wave suturing possibly the capacity of the health care system.

Waiting for the future, we shall /should take rest before a possible new wave. Psychological preparation for the teams, to be ready to do again what we have done and what have made sense, without doing again what has not been effective. Anticipation of possible time interactions between COVID and canicule during the summer, between COVID and flu during the next winter, between COVID and social wave in public hospital in the future.

7 Why did the pandemic progress differently in the countries? Did you identify some environmental, social, medical reasons?

Pr X. Lescure:

It is a difficult question, but I think that the pandemic progress depends on:

- Political reasons: time to act and duration between the epidemic phase and the time to declare the lockdown, means given in the community to test – track and isolate the first cases during the phase 2 and the post lockdown, capabilities of public health authorities for impacting in society organization and to be persuasive on behavior in the general population, level of trust of the general population in the politic decisions;
- Environmental reasons: External temperature /style of living, density of population;
- Social reasons: adherence of social distances, of mask carriage, collective cultural approaches;
- Medical reasons: capabilities and resilience of the hospital, mean age of general population, proportion of obesity in the population, proportion of other risk factors in the population, notably cardiovascular ones, management in the long-term health care facilities, possible genetic polymorphism.

8 What are the main lessons to be learned from this epidemic, for the moment?

Pr X. Lescure:

I would remind some key points:

- Efficacy of the lockdown vs adherence of the social distances
- Public health system is the main thing to reinforce in front of the pandemic
- Humility: just try to do our best in a daily approach, being aware that all we implemented at Day 1 was no more adapted at D4
- Regulation of the communication/ Psychological management of the crisis at an individual point of view but specially at a general point of view. Importance of media and social networks with benefit and worst aspects as well
- Research is a part of the riposte of the pandemic and the need to not precipitate the methods and the communication of the results
- Collectivism: a collective approach is fundamental to stay together, especially in a pandemic where global impact is so major that societal collapse is in the subconsciousness of a lot of people
- Global impact and frailty of our societies.