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Lesson Learnt by Covid-19: Going from Pandemic to Endemic Covid-19, should we Work for Diagnostic Criteria to Perform a Right Diagnosis of Covid-19 in the Future?

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Abstract

The pandemic is still on-going but with different ways if compared with first waves of COVID-19. Clinical improvements, advanced therapeutics, vaccination campaign and less virulent viral variants changed the clinical scenario. So in these last months we are observing a cohort of patients admitted in Hospital with acute illness different from fever and lung failure but that show naso pharyngeal swab positive to SARS CoV2 variant OMICRON and on the other hand other cohort of patients with asymptomatic interstitial pneumonia because a recent asymptomatic COVID-19 that should perform a thorough differential diagnosis with other causes of interstitial pneumonia. These clinical findings changed the clinical scenario and updated triage strategy are needed. Patients with lung failure could be always easily identified because associated to typical signs and symptoms have anamnestic relevant data (e.g. immunocompromised patients or antivax people or non-responders to vaccines); yet also patients without recent clinical findings of lung failure may be found with interstitial pneumonia that should be investigated with a thorough differential diagnosis including also the research of SARS CoV2 on nasopharyngeal swab or bronchoalveolar lavage. So, based on knowledge gained in these months of pandemic a strategy to perform diagnosis of COVID-19 also in absence of classic signs and symptoms should be performed taken into account utility of anamnesis, laboratory and microbiological tests and radiological findings. Should we think to adopt diagnostic criteria to perform it in next future?

Keywords: Differential Diagnosis; Interstitial Pneumonia; SARS Cov2; Lung Failure; COVID-19; COVID-Like Syndrome

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Background

Last two years have been characterized by the COVID-19 outbreak that became pandemic after few months from its identification as life-threatening disease [1-2]. Although, it may appear with different clinical pictures, the main morbidity and mortality for COVID-19 was associated to progressive lung failure due to interstitial bilateral pneumonia and following ARDS [3]. Furthermore, most common complications of lung failure from a clinical point of view have been the overlapping with bacterial or fungal infection[4] (for the contemporaneous prolonged use of antibiotics and/or viral induced lymphocytopenia) and the frequent association between COVID-19 and pulmonary embolism (PE) [5].

During the pandemic the hospitalization rate for severe COVID-19

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changed progressively because the advent of tailored therapies [6] and the advent of vaccines [7] the first ones improved the outcome of hospitalized patients while second ones reduced progressively the rate of contagion. Yet, the alert for severe COVID-19 remains because the presence of several extra troubles: first of all, the occurrence of viral variants of concern (VOCs) that testified different virulence of different viral SARS CoV2 subtypes [8] associated to the presence of a reduced rate of people at high risk to develop severe infections as anti-vax peoples or immunocompromised patients (i.e. subjects with a not adequate immunological response to vaccination).

Patients and Methods

The clinical impact to identify COVID-19 since first phases of diseases usually begins with a thorough anamnesis to be performed with triage system and its integration with objective laboratory tests and radiological imaging [2]. However as previously reported the clinical scenario progressively changing and actually we may detect COVID-19 in clinical conditions different from respiratory tract infection. So, we are able to distinguish three main sub-populations with COVID-19: patients with respiratory tract infections, patients with positive to nasopharyngeal swab (NPS) but with acute illness different from respiratory tract infection and patients with interstitial pneumonia that need an etiological evaluation of pathological causes.

Patients with respiratory tract infection

For patients that require hospitalization, the triage needs to be performed in emergency department, based on the presence of classic symptoms as cough, dyspnoea, chills associated to the presence of objective signs as reduction of pulso-oxymetry, as far as the presence of fever and their integration with anamnestic data regarding recent physical contacts with other infected peoples or with people with suggestive symptoms of COVID-19. Then, NPS with real time PCR in order to detect and to amplify viral RNA in human mucosa has been the golden standard to perform diagnosis of COVID-19 [9-11]. Yet, since first reports from China, NPS revealed a relevant quote of false negative tests, in particular among hospital workers that frequently may show COVID-like symptoms/syndrome and COVID-19 lung impairment but with normal NPS [12-16]. For this reason, someone suggested to perform further tests in patients with concrete suspect of COVID-19 also if NPS resulted negative. The research of SARS CoV2 in the bronchoalveolar lavage (BAL), in fact, has been suggested in those cases in which the clinical suspect is strong but NPS resulted negative to look for SARS CoV2 [17-18]. Furthermore, laboratory screening with early blood samples may be useful to acquire additional information: since first reports from China, in fact, COVID-19 has been associated to the increase of inflammatory markers and to clotting abnormalities. In particular, early increase of fibrinogen, C reactive protein, d-dimer, IL-6, pro-BNP and troponin acquired progressively usefulness in the daily clinical management of inpatients with COVID-19 and are able to give additional information also from a prognostic point of view [19-23]. Immunological tests as immunoglobulin's toward SARS CoV2 IG M or IG G have a positive clinical impact only if symptoms are longer than 5-6 days and in non-vaccinated people (in particular IG G).

Moreover, in patients with high suspect of COVID-19radiological imaging of lung is always needed because the specific tropism of SARS CoV2 for respiratory system, in particular for the action of viral spike protein and its link with ACE2 protein present in high concentration on the surface of cells of respiratory tract.

This combined approach (i.e. clinical suspect, microbiological and laboratory tests and radiological imaging) may be helpful to early identification of COVID-19 because interstitial pneumonia has a typical radiological "ground glass" aspect and it may be useful for early identification of patients at risk of progressive lung failure and ARDS [24, 25] and/or associated PE [26].

Patients with presence of SARS CoV2 on NPS but with medical illness different from respiratory infection

Yet, although, this combined clinical approach to identify and to stratify high risk patients affected by COVID-19 was useful to early identification of severe COVID-19 during first waves of pandemic that induced elevated rate of morbidity, mortality and hospitalization, it needs to be updated because the presence of specific SARS CoV2 VOCs as "omicron" (i.e. variant B 1.1.529) that is less virulent but more contagious and is able to induce "recurrence" with less symptoms also in people that received vaccination. In this field, a recent clinical observation from an Italian group and a following one by from another group in US, in fact, confirmed that recurrence of infection by SARS CoV2, in particular if "omicron" is present as VOC, is less associated to morbidity and mortality for lung failure [27, 28]. In this way, we are observing a time in which recurrences to SARS CoV2 infections on respiratory tract is detected at the admission in hospital for other clinical reason and acute medical illness as far as patients with acute stroke or anemia and so on. This clinical aspect induces a difficult clinical management because although VOCs of SARS CoV2 seem to have less virulence than wild type, they may be more contagious and dangerous for immunocompromised people or antivax people. So, in several hospitals, grey and specific COVID areas are now present to treat patients with SARS CoV2 detection but with acute medical illness different from respiratory tract infection.

Patients with lung dysfunction and detection of "idiopathic" interstitial pneumonia

Another unexpected scenario may be found for those patients that perform thoracic CT scan for any type of reason (e.g. follow up of pulmonary disease as far as follow up of other medical illness as far as for atypical signs and symptoms of lung diseases) with radiological evidences of ground glass areas as in case of recent COVID-19 but without anamnesis of recent infection. So, these patients may induce clinical misunderstanding in daily clinical practice: they may refer a specific symptoms escaping each type of triage system, they may have a reduced or absent viral load so escaping real Time PCR at NPS and they may show not-extended interstitial pneumonia without recent infection and/or lung failure so inducing all of us to consider a thorough differential diagnosis with other causes of interstitial pneumonia.

For these reasons, in future evaluations of interstitial pneumonia also a previous or recent infection due to SARS CoV2 should be considered and looked for with all diagnostic supports [29] (TABLE 1). In similar cases a contemporaneous disease that may induce interstitial pneumonia should be looked for. So, after the exclusion of connettivitiis (e.g. rheumatoid arthritis, systemic erythematous lupus and so) [30] and hypersensitivity pneumonitis (e.g. drug intolerance, allergy and so on) [31, 32], an evaluation of infective causes should be performed and it should include the microbiological test to identify bacteria, pests or viruses (e.g. mycoplasma, legionellaspp, pneumocystis, influenza virus) [33, 34] and to include also the research of SARS CoV2 with NPS or bronchoalveolar lavage (BAL) with real time PCR (**Table 1**).

Discussion

The memory of pandemic due to SARS CoV2 will be lasting and several issues need to be checked again in next future. The chance of VOCs that may escape vaccinations and the chance to have olygo-symptomatic COVID-19 with asymptomatic interstitial pneumonia are among these. So, becoming endemic the disease a thorough clinical evaluation of all diseases able to induce interstitial pneumonia should be ruled as far as all diseases able to suggest respiratory infections in absence of vaccination against SARS CoV2 or in presence of immunocompromised patients for any reason.

Only with this approach, a tailored therapy may be performed in shortest time and thoracic CT scan could be together to NPS or BAL the golden standard tests to do it.

Of course someone may speculate that these findings may be associate to long-COVID, but the long COVID syndrome has been identified according to NICE guidelines only with an association of symptoms and laboratory test [35], so they cannot take into account patients with unexpected interstitial pneumonia at thoracic CT scan or patients with different symptoms because the presence of a new VOC.

Therefore, since new VOCs will be find inducing new clinical signs and symptoms or suggesting new diagnostic approach we should be able to easily identify patients to high risk to develop lung failure for COVID-19 because ICP or antivax people and patients that developed interstitial pneumonia because a previous olygo-symptomatic COVID-19 but with exclusion of other diseases able to induce it (in any case the microbiological test with NPS or BAL to look for SARS CoV2 should be performed) and patients with less virulent viral variant that may induce a less severe infection but that require hospitalization for other acute medical reason.

Conclusion

So, what we need in next future in which morbidity, hospitalization and mortality for interstitial pneumonia COVID-19 will decrease? Should we forget what we lived in last two years? Of course we must remember! In particular, because COVID-19 could interest in next future immunocompromised patients and anti-Vax peoples, as already suggested: pandemic will go away from our life but we need to have clinical and diagnostic criteria of COVID-19 if it will be endemic for ICP and anti-Vax people or other frail subgroups of patients. We should include clinical suspicion based on signs and symptoms (i.e. dyspnoea, tachypnea, reduction of pulse-oximetry, fever, chills, decreased immunological power or absence of anti SARS CoV2 vaccination and recent contact with another suspected subject with similar symptoms), radiological features on thoracic CT scan (i.e. evidence of interstitial pneumonia, in this case high resolution CT scan is the golden choice) and microbiological tests (i.e. NPS and/or BAL to detect viral RNA with real time PCR), while laboratory findings may be useful also to identify subjects at risk of clinical severe complications as bacterial overlapping as far as sepsis as far as thromboembolism as far as hearth failure (**Table 2**).

Of course our speculations need on larger cohorts of patients around the world, after the confirm of first data of this wave of SARS CoV2 pandemic mainly based to VOCs B 1.1.529; yet, this clinical trend is actually present in our daily clinical life and we can assume a relevant value from it if there will be not further waves of SARS CoV2 pandemic and the endemic phase will begin and continue rendering COVID-19 effective only against selected categories as ICP and anti-vax people.

Table 1. Diseases able to induce interstitial pneumonitis.

Idiopathic or criptogenetic
Rheumatoid arthritis
Connettivitis (SLE and others)
Drug intolerance (amiodarone, chemotherapeutics and others)
Allergic alveolitiis
Acute infectious disease (SARS CoV2, pneumocystis, mycoplasma, legionella spp, influenza)

Table 2. Clinical, microbiological, laboratory and radiological features useful to perform diagnosis of COVID-19.

Major tests	Anamnestic data	Clinical signs and symptoms	Laboratory test with prognostic values
High resolution thoracic CT scan	Recent contact with another infected subject	Fever	Laboratory inflammatory markers (e.g. CRP, fibrinogen, IL-6, LDH and so on)
Real time PCR on NPS	Absence of vaccination anti-SARS CoV2	Chills/cough	d-dimer, pro BNP, troponin
Real time PCR on BAL	Immunological defects (inherited immunodeficiency, chemotherapy for cancer or transplantation, HIV, immune pathological systemic disease)	Tachypnea	Anti-SARS CoV2 IGG
-	-	Dyspnoea	Alkalosis at haemo gasanalysis
-	-	Pulso-oxymetry values < 93%	-

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