Coronavirus Diseases

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Contributor: Damiano Pizzol

At the end of 2019 a novel virus, SARS-Cov-2, causing severe acute respiratory syndrome has expanded from Wuhan, China. In March 2020 the World Health Organization declared the SARS-Cov-2 virus a global pandemic. We performed a narrative review to describe existing literature with regard to COVID-19 epidemiology, pathophysiology, diagnosis, management and future perspective. MEDLINE, EMBASE and Scopus databases were searched for relevant articles.Although only when the pandemic will end it will be possible to assess the health, social and economic impact of this global disaster, this review represents a picture of the current state of the art. In particular, we focus on public health impact, pathophysiology and clinical manifestations, diagnosis, case management, emergency response and preparedness.

Keywords: coronavirus ; covid-19 ; pathogenesis ; preparedness ; emergency ; pandemic

1. Introduction

To address the pathogenetic mechanisms of SARS-CoV-2, its viral structure and genome must be considered. Coronaviruses are enveloped positive strand RNA viruses with the largest known RNA genomes—30–32 kb—with a 5′-cap structure and 3′-poly-A tail. Starting from the viral RNA, the synthesis of polyprotein 1a/1ab (pp1a/pp1ab) in the host is realized[1]. The transcription works through the replication-transcription complex (RCT) organized in double-membrane vesicles and via the synthesis of subgenomic RNAs (sgRNAs) sequences. Of note, transcription termination occurs at transcription regulatory sequences, located between the so-called open reading frames (ORFs) that work as templates for the production of subgenomic mRNAs[2]. In the atypical CoV genome, at least six ORFs can be present. Among these, a frameshift between ORF1a and ORF1b guides the production of both pp1a and pp1ab polypeptides that are processed by virally encoded chymotrypsin-like protease (3CLpro) or main protease (Mpro), as well as one or two papain-like proteases for producing 16 non-structural proteins (nsps)[2]. Apart from ORF1a and ORF1b, other ORFs encode for structural proteins, including spike, membrane, envelope, and nucleocapsid proteins and accessory proteic chains[1][2]. Different CoVs present special structural and accessory proteins translated by dedicated sgRNAs. Pathophysiology and virulence mechanisms of CoVs, and therefore also of SARS-CoV-2 have links to the function of the nsps and structural proteins. For instance, research has underlined that nsps are able to block the host innate immune response[3]. Among the functions of the structural proteins, the envelope has a crucial role in virus pathogenicity as it promotes viral assembly and release.

2. Pathophysiology and Clinical Manifestation

The pathogenic mechanism that produces pneumonia seems to be particularly complex[1][2][3]. The data so far available seem to indicate that the viral infection is capable of producing an excessive immune reaction in the host. In some cases, a reaction takes place, which as a whole is labelled a “cytokine storm”. The effect is extensive tissue damage. The protagonist of this storm is interleukin 6 (IL-6). IL-6 is produced by activated leukocytes and acts on a large number of cells and tissues[4]. It is able to promote the differentiation of B lymphocytes, promotes the growth of some categories of cells, and inhibits the growth of others. It also stimulates the production of acute phase proteins and plays an important role in thermoregulation, in bone maintenance and in the functionality of the central nervous system[5]. Although the main role played by IL-6 is pro-inflammatory, it can also have anti-inflammatory effects. In turn, IL-6 increases during inflammatory diseases, infections, autoimmune disorders, cardiovascular diseases and some types of cancer[6]. It is also implicated into the pathogenesis of the cytokine release syndrome (CRS) that is an acute systemic inflammatory syndrome characterized by fever and multiple organ dysfunction[7].

The virus might pass through the mucous membranes, especially nasal and larynx mucosa, then enters the lungs through the respiratory tract. Then the virus would attack the targeting organs that express angiotensin converting enzyme 2 (ACE2), such as the lungs, heart, renal system and gastrointestinal tract[5][6][7]. The virus begins a second attack, causing the patient’s condition to aggravate around 7 to 14 days after onset. B lymphocyte reduction may occur early in the

disease, which may affect antibody production in the patient. Besides, the inflammatory factors associated with diseases mainly containing IL-6 were significantly increased, which also contributed to the aggravation of the disease around 2 to 10 days after onset.

The clinical spectrum of COVID-19 varies from asymptomatic or paucisymptomatic forms to clinical conditions characterized by severe respiratory failure that necessitates mechanical ventilation and support in an intensive care unit (ICU), to multiorgan and systemic manifestations in terms of sepsis, septic shock, and multiple organ dysfunction syndromes (MODS)[8]. Asymptomatic infections have also been described, but their frequency is unknown. The main symptoms are reported in Table 1. Pneumonia appears to be the most frequent serious manifestation of infection, characterized primarily by fever, cough, dyspnea, and bilateral infiltrates on chest imaging.[9] There are no specific clinical features that can yet reliably distinguish COVID-19 from other viral respiratory infections. Other, less common symptoms have included headaches, sore throat, and rhinorrhea. In addition to respiratory symptoms, gastrointestinal symptoms (e.g., nausea and diarrhea) have also been reported, and in some patients they may be the presenting complaint. Respiratory droplet transmission is the main route and it can also be transmitted through person-to-person contacts by asymptomatic carriers[8][9].

Table 1. Main COVID-19-associated symptoms.

Fever
Cough
Dyspnea
Headach
Sore throat
Rhinorrhea

Chest CT in patients with COVID-19 most commonly demonstrates ground-glass opacification with or without consolidative abnormalities, consistent with viral pneumonia[10]. Chest CT abnormalities are more likely to be bilateral, have a peripheral distribution, and involve the lower lobes. Less common findings include pleural thickening, pleural effusion, and lymphadenopathy[11]. Chest CT may be helpful in making the diagnosis, but no finding can completely rule in or rule out the possibility of COVID-19. The possibility of COVID-19 should be considered primarily in patients with new onset fever and/or respiratory tract symptoms (e.g., cough, dyspnea)[10][11][12]. It should also be considered in patients with severe lower respiratory tract illness without any clear cause. Although these syndromes can occur with other viral respiratory illnesses, the likelihood of COVID-19 is increased if the patient[13]: (1) resides in or has travelled within the prior 14 days to a location where there is community transmission of SARS-CoV-2 (i.e., large numbers of cases that cannot be linked to specific transmission chains); (2) has had close contact with a confirmed or suspected case of COVID-19 in the prior 14 days, including through work in health care settings. Close contact includes being within approximately six feet (about two meters) of a patient for a prolonged period of time while not wearing personal protective equipment or having direct contact with infectious secretions while not wearing personal protective equipment.

The period from the onset of COVID-19 symptoms to death ranges from 6 to 41 days with a median of 14 days[14]. This period is dependent on the age of the patient and status of the patient's immune system. It was shorter among patients >70-years old compared with those under the age of 70 years. The most common symptoms at onset of COVID-19 illness are fever, cough, and fatigue, while other symptoms include sputum production, headache, haemoptysis, diarrhoea, dyspnoea, and lymphopenia[13].

The WHO has reported an incubation period for COVID-19 between 2 and 10 days. However, some literature suggests that the incubation period can last longer than two weeks and it is possible that a very long incubation period could reflect double exposure[13]. Many studies support a 14-day medical observation period for people exposed to the pathogen. The

severity of the clinical picture seems to be correlated with age (>70 years), comorbidities such as: diabetes, chronic obstructive pulmonary disease (COPD), hypertension, obesity and male sex but currently no scientifically valid explanations have been developed[14][15][16].

References

1. Jian Lei; Yuri Kusov; Rolf Hilgenfeld; Nsp3 of coronaviruses: Structures and functions of a large multi-domain protein. *Antiviral Research* **2018**, *149*, 58-74, 10.1016/j.antiviral.2017.11.001.
2. Michael Letko; Andrea Marzi; Vincent Munster; Functional assessment of cell entry and receptor usage for SARS-CoV-2 and other lineage B betacoronaviruses. *Nature Microbiology* **2020**, *5*, 562-569, 10.1038/s41564-020-0688-y.
3. Cascella, M.; Rajnik, M.; Cuomo, A.; Dulebohn, S.C.; Di Napoli, R. Features, evaluation and treatment coronavirus (COVID-19). In StatPearls; StatPearls Publishing: Treasure Island, FL, USA, 2020. Available online: http://www.ncbi.nlm.nih.gov/books/NBK554776/ (accessed on 31 March 2020).
4. Chloe J. Pyle; Faith Uwadiae; David P. Swieboda; James A. Harker; Early IL-6 signalling promotes IL-27 dependent maturation of regulatory T cells in the lungs and resolution of viral immunopathology. *PLOS Pathogens* **2017**, *13*, e1006640, 10.1371/journal.ppat.1006640.
5. C Chen; X R Zhang; Z Y Ju; W F He; [Advances in the research of cytokine storm mechanism induced by Corona Virus Disease 2019 and the corresponding immunotherapies].. *Zhonghua Shao Shang Za Zhi* **2020**, *36*, E005, .
6. Francesco Bennardo; Caterina Buffone; Amerigo Giudice Md; New therapeutic opportunities for COVID-19 patients with Tocilizumab: Possible correlation of interleukin-6 receptor inhibitors with osteonecrosis of the jaws.. *Oral Oncology* **2020**, *null*, 104659, 10.1016/j.oraloncology.2020.104659.
7. Stefan Rose-John; Interleukin-6 Family Cytokines. *Cold Spring Harbor Perspectives in Biology* **2018**, *10*, a028415, 10.1101/cshperspect.a028415.
8. Tommaso Lupia; Silvia Scabini; Simone Mornese Pinna; Giovanni Di Perri; Francesco Giuseppe De Rosa; Silvia Corcione; 2019-novel coronavirus outbreak: A new challenge. *Journal of Global Antimicrobial Resistance* **2020**, *21*, 22-27, 10.1016/j.jgar.2020.02.021.
9. Yongshi Yang; Fujun Peng; Runsheng Wang; Kai Guan; Taijiao Jiang; Guogang Xu; Jinlyu Sun; Christopher Chang; The deadly coronaviruses: The 2003 SARS pandemic and the 2020 novel coronavirus epidemic in China. *Journal of Autoimmunity* **2020**, *109*, 102434, 10.1016/j.jaut.2020.102434.
10. Tao Ai; Zhenlu Yang; Hongyan Hou; Chenao Zhan; Chong Chen; Wenzhi Lv; Qian Tao; Ziyong Sun; Liming Xia; Correlation of Chest CT and RT-PCR Testing in Coronavirus Disease 2019 (COVID-19) in China: A Report of 1014 Cases. *Radiology* **2020**, *null*, null, 10.1148/radiol.2020200642.
11. Li, Y.; Xia, L.; Coronavirus disease 2019 (COVID-19): Role of chest CT in diagnosis and management. *AJR Am. J. Roentgenol.* **2020**, *null*, 1–7, .
12. Harrison X. Bai; Ben Hsieh; Zeng Xiong; Kasey Halsey; Ji Whae Choi; Thi My Linh Tran; Ian Pan; Lin-Bo Shi; Dong-Cui Wang; Ji Mei; et al. Performance of radiologists in differentiating COVID-19 from viral pneumonia on chest CT. *Radiology* **2020**, *null*, 200823, 10.1148/radiol.2020200823.
13. World Health Organization Covid 19 Infection. Available online: https://www.who.int/emergencies/diseases/novel-coronavirus-2019 (accessed on 31 March 2020).
14. Chaomin Wu; Xiaoyan Chen; Yanping Cai; Jia'An Xia; Xing Zhou; Sha Xu; Hanping Huang; Li Zhang; Xia Zhou; Chunling Du; et al. Risk Factors Associated With Acute Respiratory Distress Syndrome and Death in Patients With Coronavirus Disease 2019 Pneumonia in Wuhan, China. *JAMA Internal Medicine* **2020**, *null*, null, 10.1001/jamainternmed.2020.0994.
15. Fei Zhou; Ting Yu; Ronghui Du; Guohui Fan; Ying Liu; Zhibo Liu; Jie Xiang; Yeming Wang; Bin Song; Xiaoying Gu; et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. *The Lancet* **2020**, *395*, 1054-1062, 10.1016/s0140-6736(20)30566-3.
16. Wenzheng Han; Bin Quan; Wei Guo; Jun Zhang; Yong Lu; Gang Feng; Qiwen Wu; Fang Fang; Long Cheng; Nanlin Jiao; et al. The course of clinical diagnosis and treatment of a case infected with coronavirus disease 2019.. *J. Med. Virol.* **2019**, *92*, 461–463, .