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EDITORIAL

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The novel Chinese coronavirus (2019-nCoV) infections: Challenges for fighting the storm

Since end of December 2019, a cluster of patients with pneumonia of unknown origin was reported from Wuhan, Hubei province, China.[1] They shared a connection with the Huanan South China Seafood Market in Wuhan, and now it has been confirmed that the disease is caused by a novel coronavirus (provisionally named 2019-nCoV).[1] As of today (30 January 2020), 7734 cases have been confirmed in China, and 90 cases have also been cumulatively reported from Taiwan, Thailand, Vietnam, Malaysia, Nepal, Sri Lanka, Cambodia, Japan, Singapore, Republic of Korea, United Arab Emirate, United States, The Philippines, India, Australia, Canada, Finland, France and Germany (Finland, France and Germany are the only European countries in which cases [n = 1, n = 5, and n = 4, respectively] have been reported up to date). According to the released news, the case rate fatality is 2.2% (170/7824).[2]

Coronavirus are enveloped, positive-strand RNA viruses, that may be transmitted to humans from intermediate hosts (usually peridomestic mammals) and with bats being the likely reservoir of most of them, in view of the observed virus diversity.[3] The 2019-nCoV is the seventh coronavirus known to infect humans. Four (229E, NL63, OC43 and HKU1) are responsible for mild upper respiratory tract infections (common cold), whereas the severe acute respiratory syndrome coronavirus (SARS-CoV, which has been contained[4]) and the Middle East respiratory syndrome coronavirus (MERS-CoV) are able to cause atypical pneumonia. This difference in the achievable sites of infection likely depends on the presence in the lower respiratory tract of angiotensin-converting enzyme 2 (ACE2) and dipeptidyl peptidase 4, which are the main human receptors of the surface glycoprotein S of SARS-CoV and MERS-CoV, respectively.[3] Phylogenetically, the 2019-nCoV is closer to the SARS-CoV than to the MERS-CoV, and it has been suggested to interact with the same main host receptor (ACE2), albeit possibly with lower binding affinity.[1,5] Nonetheless, both this finding (considering also that the NL63-CoV, which causes upper respiratory tract infections, interacts with ACE2[4]) and other aspects of the pathogenesis of 2019-nCoV infection deserve further investigation to be thoroughly elucidated.

The clinical description of the first 41 patients with 2019-CoV pneumonia has been recently published.[6] Their median age was 49 (interquartile range 41-58), and 73% were males (30/41). Direct exposure to the Huanan Seafood Market was registered in 66% of cases (27/41).[6] The most common symptoms were fever (40/41, 98%) and cough (31/41, 76%). Dyspnoea was present in 55% of patients (22/40, missing = 1), and 13/41 (32%) required admission to the intensive care unit (ICU). Computerized tomography showed bilateral pulmonary involvement in 98% of cases, with the typical findings being multiple areas of consolidation and bilateral ground-glass opacity. Secondary bacterial infections (pneumonia or bloodstream infection) developed in 4 patients (10%). The laboratory results showed leukopenia and lymphopenia in 25% and 63% of patients, respectively, with procalcitonin being normal (<0.1 ng/mL) in 69% of them. Increased serum levels of IL1B, IFNγ, IP10 and MCP1 were registered in the study population compared with healthy subjects, and higher levels of GCSF, IP10, MCP1, MIP1A and TNFα were measured in ICU than in non-ICU 2019-nCoV patients, suggesting a possible role of pro-inflammatory cytokines in influencing disease severity. On the other hand, an increased release of anti-inflammatory markers such as IL4 and IL10 was also measured in 2019-nCoV patients, differently from what previously observed for SARS-CoV, a finding that needs to be confirmed in larger cohorts. Of note, a laboratory diagnosis of virus-related cardiac injury by means of increased hypersensitive troponin I levels was made in 5/41 patients (12%). The overall case fatality rate was 15% (6/41).[6] A tentative comparison of the clinical presentation (according to the first available data) of 2019-nCoV infection with those of SARS-CoV and MERS-CoV infections is presented in Table 1.

This first clinical report is useful for highlighting some key issues surrounding both the emergence and the management of the 2019-nCoV that are currently being investigated by experts worldwide. The first is the search for a reservoir and/or an intermediate host from which the infection spread to humans. Two species of snakes have been proposed as the possible wildlife reservoir of the 2019-nCoV on the basis of the virus codon using pattern,[8] although other researchers remain sceptical, stating that there is no consisting evidence of coronavirus reservoirs other than mammals and birds, and indicating that mammals are the most likely link between 2019-nCoV and humans.[9] The fact that many (66%) but not all of the 41 clinical cases were exposed to the Huanan Seafood

TABLE 1 Clinical presentation of 2019-nCoV, SARS-CoV and MERS-CoV infections according to published series

Virus	2019-nCoV[a]	SARS-CoV	MERS-CoV
Mean incubation time	3-6 d[13]	5 d[11]	5 d[11]
Clinical presentation	Fever (98%), cough (76%) and dyspnoea (55%) were the most frequent signs and symptoms.[6] Diarrhoea observed only in 3% of patients.[6]	Fever (99%-100%), cough (62%-100%), and chills or rigour (15%-73%) were the most frequent signs and symptoms.[11] Shortness of breath and diarrhoea observed in 40%-42% and 20%-25% of patients, respectively.[11]	Fever (98%), chills or rigor (87%), and cough (83%) were the most frequent signs and symptoms.[11] Shortness of breath and diarrhoea observed in 72% and 26% of patients, respectively.[11]
Laboratory markers	Leukopenia (25%), lymphopenia (63%), thrombocytopenia (5%), high lactate dehydrogenase (73%).[6]	Leukopenia (25%-35%), lymphopenia (68%-85%), thrombocytopenia (40%-45%), high lactate dehydrogenase (50%-71%)[11]	Leukopenia (14%), lymphopenia (32%), thrombocytopenia (36%), high lactate dehydrogenase (48%)
Radiology	CT abnormalities (100%).[6] Reported typical findings are bilateral multiple lobular and subsegmental areas of consolidation in ICU patients and bilateral ground-glass opacity and subsegmental areas of consolidation in non-ICU patients.[6]	Chest radiography or CT abnormalities (94%-100%). Reported typical findings were unilateral/bilateral ground-glass opacities or focal unilateral/bilateral consolidation. Abnormalities tended to progress to bilateral consolidation in hospitalized patients	Chest radiography or CT abnormalities (90%-100%).[11] Reported typical findings are unilateral/bilateral patchy densities or infiltrates, bilateral hilar infiltration, segmented/lobar opacities, ground-glass opacities, and possible small pleural effusions. Lower lobes generally more affected than upper lobes early in the course of illness and more rapid radiographic progression than SARS.[11]

Abbreviations: CoV, coronavirus; CT, computerized tomography; ICU, intensive care unit; MERS, Middle East respiratory syndrome; SARS, severe acute respiratory syndrome.

[a]Reported information from 2019-hCoV is from the first published series of 41 hospitalized patients.[6]

Market introduces another important issue, that is, the possibility of human-to-human transmission besides exposure to infected animals. A human-to-human transmission through virus-laden aerosols was confirmed for SARS-CoV.[10] With regard to 2019-nCoV, a similar possibility is in line with the fact that not all the reported cases were directly exposed to the Huanan Seafood market, and also with the observation that some cases occurred in healthcare workers.[6] In addition, the existence of a self-sustained human-to-human transmission is supported by the analyses of the Imperial College London, UK, conducted using a mathematical model of transmissibility.[7] Their most recent estimation (which will be likely updated and refined according to the future trajectory of the outbreak) is that each case infected on average 2.6 other people (uncertainty range 1.5-3.5), with the possibility of a self-sustaining human-to-human transmission being the only plausible explanation for the scale of the outbreak in Wuhan. They also estimated that blocking over 60% of transmission would be necessary for infection-control measures to effectively control the outbreak.[7] The question that remains is whether asymptomatic subjects incubating the infection and cases with relatively mild symptoms (those with an influenza-like syndrome neither necessitating nor searching for care) are able to effectively transmit the virus to other humans, since this may complicate or delay the effectiveness of infection-control measures. On the other hand, a large pool of mild cases could explain the currently reported low case fatality rate (2.2%) in press news, which is lower than the case fatality rate observed in the hospitalized patients with pneumonia described in the published report (15%),[2,6] which probably better represents the subpopulation of patients with the most severe clinical presentation rather than the entire population of 2019-nCoV-infected patients, in which the overall crude mortality is likely lower. Worth noting is also that the case fatality rate of 2019-nCoV reported in the press news is lower than those previously described for SARS-CoV and MERS-CoV infections (9.5% and 40%, respectively[11]). Finally, the promising effect observed in animal models of SARS-CoV and MERS-CoV infections of antivirals such as remdesivir and lopinavir/ritonavir is guiding their evaluation against 2019-nCoV (a randomised controlled trial to assess the efficacy and safety of lopinavir/ritonavir in hospitalized patients with 2019-nCoV infection has been initiated in China).

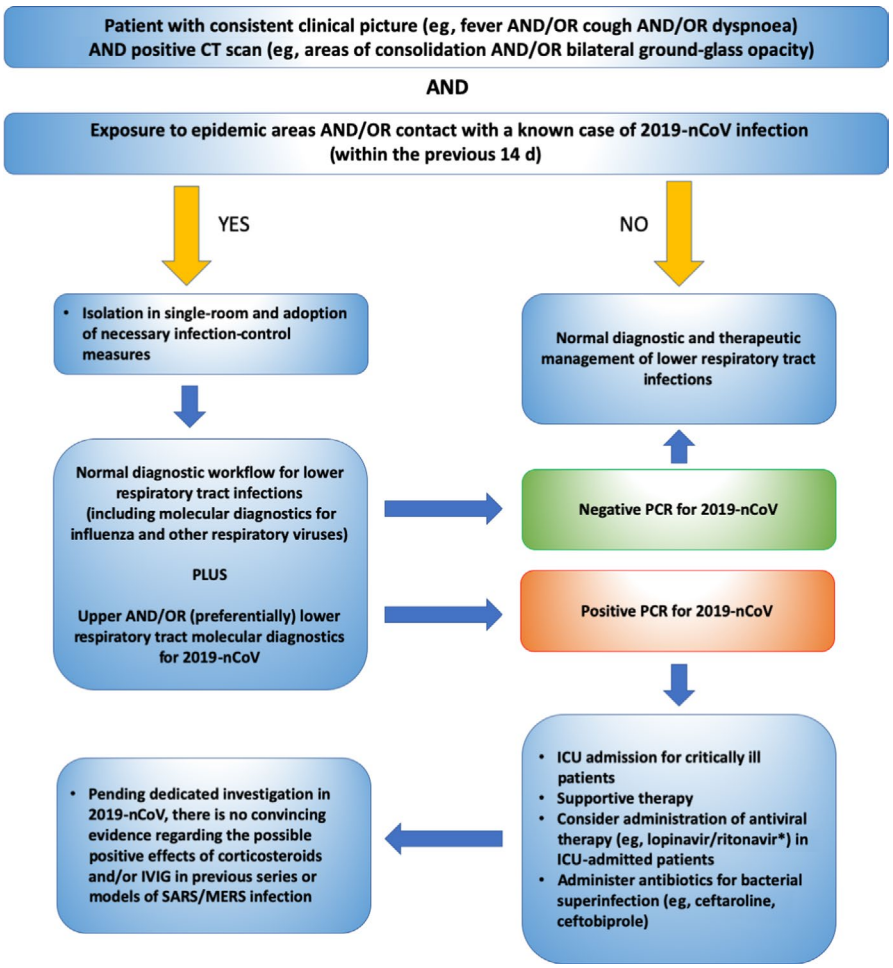

FIGURE 1 Possible diagnostic/therapeutic algorithm according to currently available information in patients with suspected 2019-nCOV pneumonia. Abbreviations: CoV, coronavirus; ICU, intensive care unit; IVIG, intravenous immunoglobulin; PCR, polymerase chain reaction. *Currently, there is no a standardized therapeutic recommendation. Lopinavir/ritonavir is available in several hospitals and has shown promising results in pre-clinical models and case series of SARS-CoV and MERS-CoV infections,[14,15] although no high-level evidence of efficacy and safety is currently available for its use either as monotherapy or in combination with interferons or other drugs (a randomized controlled trial has been initiated in patients with 2019-nCoV pneumonia in China).[6] Conflicting results have been reported in previous experiences of using ribavirin for severe pulmonary infections caused by coronaviruses, whereas promising pre-clinical models exist for remdesivir and for IFNβ1b.[3,14,15] Drugs approved for other indications such as loperamide, chloroquine, chlorpromazine, cyclosporin A and mycophenolic acid have shown activity against coronavirus in vitro, but their role in the therapy of the human disease remains debatable (also in view of the immunosuppressive effect of cyclosporin A and mycophenolic acid).[14,15] Although again in the absence of high-level evidence, the use of plasma from convalescent patients could be considered following previous experiences in MERS-CoV-infected subjects,[15] preferably after dedicated investigation in 2019-nCoV patients

Further elucidating all these aspects is critical for perfectionating both the containment of transmission and the clinical approach to patients with 2019-nCoV infection (a tentative algorithm for the clinical approach to severe cases is proposed in Figure 1). This should add to the already occurred very rapid and concerted response to this rapidly evolving outbreak by both local and global authorities and organizations, and by researchers in China and worldwide, with the overall results that important information about the characteristics of the virus is rapidly becoming available, and may improve both containment and management efforts. For example, the genome of 2019-nCoV has been sequenced (and publicly shared) in a very few days, molecular diagnostic platforms for identifying 2019-nCoV have been rapidly developed, and the time needed for developing a vaccine is expected to be shorter than 3.25 months (compared with 20 months at the time of the SARS-CoV outbreak).[1,3,12,13] As recently highlighted by Anthony Fauci and colleagues,[3] although the true trajectory of this outbreak is still impossible to be predicted, such rapid, globally concerted and prepared responses (also in terms of clinical management) remain essential to effectively counteract novel emerging viral infections. In this regard, it is likely that there will be other cases in Europe and ensuring firm and timely detection and

management is essential to retain their number limited and their occurrence sporadic.

CONFLICT OF INTEREST

Outside the submitted work, MB serves on scientific advisory boards for Angelini, AstraZeneca, Bayer, Cubist, Pfizer, Menarini, MSD, Nabriva, Paratek, Roche, Shionogi, Tetraphase, The Medicine Company and Astellas Pharma Inc and has received funding for travel or speaker honoraria from Algorithm, Angelini, Astellas Pharma Inc, AstraZeneca, Cubist, Pfizer, MSD, Gilead Sciences, Menarini, Novartis, Ranbaxy, Teva. Outside the submitted work, DRG reports an unconditional grant from MSD Italia and honoraria from Stepstone Pharma GmbH.

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