Review
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Novel coronavirus disease-2019: Epidemiology, diagnosis, therapeutics and guideline protocol for disease management in different countries

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Abstract

Objectives Coronavirus is a positive-strand RNA virus, which consists of a certain virus that infects both animals and humans; including the recent one which is known as severe acute respiratory syndrome coronavirus (SARS-CoV). Coronavirus has been a significant threat in November 2019.

Methods The review focus on full coverage of the epidemic state of the virus worldwide, major diagnostic approaches used, the therapeutic drugs types and approaches used, the pathology and pathogenesis of the disease in infected patients, and its consequences in addition to the virus and the major guidelines for the disease management in different countries. Different literature and guidelines among different databases were searched. Literature review was conducted using the following search engines: Google Scholar, Medline, Pub Med, Web of Science, and Science Direct, in order to better reveal the published peer-reviewed articles about SARS-CoV, MERS-CoV, and 2019-nCoV.

Results SARS-CoV data collected in this review will give help to medical researchers and further decision-makers, social and economic makers concerned with health status, and pandemic infections among countries in different aspects. As per understanding, the disease and the different responses to this virus could help to find immune-based therapeutics or/and traditional medicines. By June 1, 2020, the pandemic cases are about six million worldwide and the number is rising everyday sharply. While the actual and accurate causes and effective treatment of COVID-19 are still unknown or unavailable and the number of active cases of the infection is rising every day causing rising panic and concern on public health worldwide. The greatest number of new cases and deaths of COVID-19 were reported in the USA, Brazil, Russia, Spain, the UK, Italy, Germany, and France. This growing number of cases is due to the person-to-person transmission that has been reported both in and outside of China. In Palestine, the pandemic cases were about 600 by the end of May 2020. In June 28, 2020 coronavirus cases were 10,088,576, deaths 501,442, and recovered 5,466,534 globally. The cases increased very sharply within a short period (about three weeks); in Palestine, the spread of the disease is also nearly tripled by this time (1,815 cases reported). The outbreak of the disease is extremely very fast as by the end of June (within only one month period), the cases have been nearly doubled as the coronavirus cases confirmed were 10,690,566, deaths 516,393 (8%), and recovered are 5,856,464 worldwide. The high incidence rate and cases were also in the USA (2,751,571), then Brazil (1,426,913), Russia (654,405), etc. In Palestine by this time, at the end of June, the reported cases were increased very sharply by about six times; as more than 3,095 cases were reported including East Jerusalem (337 cases), with 11 deaths. The highest cases (1947 cases) were in Hebron Governorate; with these confirmed cases Palestine ranked 97 among 215 countries that have coronavirus; with the highest outbreak rate in the world; compare to population number.

Conclusion The pandemic by COVID-19 is a very dangerous issue affecting people worldwide. Without fundamental therapeutic interventions, current management is to reduce the virus spread and provide supportive care for diseased patients. There is an urgent need to develop targeted therapies. Understanding the disease and the different responses to this virus could help to find immune-based therapeutics or/and traditional medicines. It is important to have the latest information but we must ensure that information is coming from trustworthy sources. We have collected a variety of helpful resources related to COVID-19. We also have several initiatives to get the public involved in our work and educated on how to make informed health decisions. The global impact of this new pandemic is yet uncertain.

Keywords Coronavirus, SARS-CoV, Pandemic, Pathogenesis, Diagnostics, Therapeutics

Introduction

A group of pneumonia cases of unidentified etiology was stated in Wuhan, Hubei Province, China, on December 31, 2019, Afterwards, China reported a novel coronavirus on January 9, 2020, and this was the contributing agent of this outbreak. Coronavirus disease 2019 (COVID-19), which is called severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), is a novel strain of coronavirus that has not been previously recognized in humans[1]. Until 15 April 2020, the emerging Coronavirus had spread nearly all over the world, with differences in disease severity among different countries and different patients

In general, Coronaviruses are among the family of enveloped positive-sense RNA viruses fluctuating between 60 and 140 nm in diameter, with spike-like projections giving it a crown-like appearance under the electron microscope; hence the name Coronavirus. Despite all ages are vulnerable, the infection majorly spreads and gets transmitted through large droplets as in coughing and sneezing by symptomatic patients. Patients can be infectious for as long as the signs last, and even on clinical recovery. Some people may act as super transmitters. The virus can persist viable on planes for days, in favorable atmospheric conditions, despite it is damaged in less than a minute by communal disinfectants like sodium hypochlorite, hydrogen peroxide, etc. The infection is mainly attained both *via* inhalation of these droplets or *via* touching polluted surfaces then touching the nose, mouth, and eyes. Infection in neonates, infants, and children, has been also described to be significantly milder than their adult counterparts. The most popular symptoms were fever (50%) and cough (38%).[2–10]

We conducted a literature review of publicly available information to summarize knowledge about the pathogen and the current epidemic. Understanding the disease and the

different responses to this virus could help to find immune-based therapeutics or/ and traditional medicines.

Methodology

The methodology aspects for this literature review were conducted as the following: the different literature and guidelines among different databases were searched. Literature reviewing was conducted using the following search engines: Google Scholar, Medline, Pub Med, Web of Science, and Science Direct, so in order to better reveal the published peer-reviewed articles about SARS-CoV, MERS-CoV, and 2019-nCoV.

The following initial terms used were "2019-nCoV" OR "2019 novel coronavirus" OR "SARS CoV-2" OR "COVID-19" OR "coronavirus disease 2019" OR "NCP" OR "Novel coronavirus pneumonia" to match with the article title, abstract, or topic. Additionally, further search words with above keywords as "SARS" OR "SARS-CoV" OR "severe acute respiratory syndrome", "MERS" OR "MERS-CoV" OR "middle east respiratory syndrome", in combinations of with "spike protein" OR "genome" OR "reproductive number" OR "incubation period" OR "fatality rate" OR "clinical characteristics" OR "pathology" OR "autopsy" OR "treatment" OR "prevention", were used Moreover, the already released official documents by the World Health Organization (WHO) were accessed for searching and keeping up to date data on COVID-19. Only English versions of articles were used and included in this literature review.

The review includes publicly available information about the knowledge about the diseases that were discussed. The limitations of this study review are that the numbers are possibly an underestimate of the infected and dead and based on the available information published. Besides the accurate information about the disease and the virus including the origin of the virus, the symptoms are varied and changing from time to time. For example, it is thought that the SARS-CoV-2 originated from bats, the intermediary animal through which it crossed over to humans is uncertain. Pangolins and snakes are the current suspects.

The importance of this review, as in the ever-changing situation that we are in, it's important to have the latest information but we must ensure that information is coming from trustworthy sources. We have collected a variety of helpful resources related to COVID-19. We also have several initiatives to get the public involved in our work and educated on how to make informed health decisions.

Results and discussions

Pathological changes cause by Coronavirus

The pathological changes from postmortems and biopsies are described below.

1. **Lungs:** Among the lungs, pulmonary consolidation of variable degrees was intra-alveolar serous fluids, fibrinous exudates, and hyaline-membrane development are present. Exudate contains primarily mononuclear macrophages and multinucleated giant cells are communal. Moreover, inclusion bodies can be found within type II pneumocytes and macrophages. Alveolar congestion and edema can be realized, the formation of hyaline thrombus in blood vessels is evident.[11,12]
2. **Spleen, hilar lymph node, and bone marrow:** The size of the spleen is significantly decreased and the lymphocytes number is considerably reduced. Focal hemorrhage and necrosis due exist. Macrophage hyperplasia and phagocytosis can be detected in the spleen. In the lymph nodes, the count of lymphocytes is decreased; some necrosis can be found. A decline of CD4+ T cells and CD8+ T cells can be noticed in both the spleen and the lymph nodes by IHC. Trilineage hematopoiesis is decreased in the bone marrow.[12]
3. **Heart and blood vessel:** Deterioration and necrosis can be found in cardiomyocytes. Interstitial infiltration of a slight number of monocytes, lymphocytes and/or neutrophils can be realized, endothelial inflammation and thrombus detected in specific vessels
4. **Kidney: Exudate:** Full of proteins can be found within the glomerular capsule. Degeneration and desquamation of renal tubular epithelium are existent. Hyaline casts can be realized. Interstitial congestion, microthrombi, and focal fibrosis can be found.[12]

Seasonality of COVID-19

The seasonality of coronaviruses might be determined, in part, by environmental circumstances and host vulnerability because coronaviruses are more stable under low and mid-range relative moisture (20–50%), when defense mechanisms of the airways are also inhibited.[10]

Current studies of the continuing outbreaks appear to point out that the infection transmission is in part a role of temperature and moisture spread strength appears to decline with a rise in temperature and relative moisture. Initial analyses of the COVID-19 burst in China show the high reproductive numbers which are elucidated not only in dry, cold regions but also in tropical regions with high absolute moisture, like in Guangxi and Singapore.

Recently, there is only conditional confirmation that SARS-CoV-2 will exhibit noticeable winter seasonality in the Northern hemisphere, comparable to other human coronaviruses.[5,10]

Survival in the environment

The environmental stability of viable *SARS-CoV-2* is up to 3 h in the air after the aerosolization process up to 4 h on copper, up to 1 day on paper, wood, and up to 2–3 days on plastic and stainless steel, a recent publication indicated that the virus was more stable on flat surfaces, with the discovery of infectious virus on medical mask material for up to 7 days. At 4°C, the virus was stable up to 14 days but deactivated after 5 min at 70°C. Virus was identified most frequently on gloves, but infrequently on eye safety devices.[9,10] Screening and triage: Early recognition of patients with SARI related to COVID-19.

Screening and triage: The purpose of triage is to recognize and separate all patients with assumed COVID-19 at the initial point of connection within the health-care system (i.e., emergency department or outpatient health center). Considering COVID-19 as a probable etiology of patients with an acute respiratory infection under definite circumstances as shown in Table 1. Triage patients consume uniform triage tools and begin emergency therapy based on disease severity.[13]

Table 1. **Definition of a patient with COVID-19.**

SARI	**An ARI with a history of fever or measured temperature ≥38°C and cough start within the last ten days and necessitating hospitalization.**
Surveillance case definitions for SARI	1. SARI is a person, with history of fever and cough necessitating admittance to the hospital, with no other etiology that completely describes the clinical presentation[1] (clinicians should also be attentive to the probability of unusual presentations in immune-compromised patients) AND any of the following: a) A history of international travel in 14 days prior to symptom onset; or b) the disease happens in a health-care worker who has been working in an environment where patients with severe acute respiratory infections are being cared for, without regard to place of residence or history of travel; or c) the person develops an unusual or unexpected clinical course, especially sudden deterioration despite appropriate treatment, without regard to the place of residence or history of travel, even if another etiology has been identified that fully explains the clinical presentation 2. A person with acute respiratory illness of any degree of severity who, within 14 days before the onset of illness, had any of the following exposures: a) close physical contact[2] with a confirmed case of COVID-19 infection, while that patient was symptomatic; or b) a health-care facility in a country where hospital-associated COVID-19 infections have been reported.

(1) Testing should be consistent with local guidance for the management of community-acquired pneumonia. Samples of other etiologies involve *Streptococcus pneumonia, Haemophilus influenza type B, Legionella pneumophila*, other familiar principal bacterial pneumonia, influenza viruses, and respiratory syncytial virus.
(2) Close contact is defined as:
- Health-care-related contact, involving the provision of direct care for COVID-19 patients, working with health-care workers (HCWs) diseased with COVID-19, visiting patients, or staying in close location to the COVID-19 patients.
- Working together in close proximity or using the same classroom environment with a COVID-19 patient.
- Traveling together with COVID-19 patients in any sort of transportation.
- Living in the same home with COVID-19 patients.

The majority of patients are older than 50 years of age with the mean age is much older than patients diseased with H1N1 or with the Middle East respiratory syndrome (MERS).[8] Approximately, 30–50% of COVID-19 patients had long-lasting co-morbidities. The interval from the first symptom to respiratory failure in most patients is greater than 1 week, which is more extended than H1N1.[9] Moreover, a lot of patients go on to suffer from respiratory failure had hypoxemia but lacking signs of respiratory distress, particularly in the old patients ("silent hypoxemia").

In addition, only a smaller number of patients have additional organ dysfunction (e.g., shock, acute kidney injury) before emerging respiratory failure. These features presumably due to the fact that old-fashioned approaches (i.e., quick sequential organ failure assessment (qSOFA) score, New Early Warning Score (NEWS)) may not aid in the prediction of those patients who will go on to suffer from respiratory failure. Consequently, it is critical to institute an expectation or primary recognition model of patients expected to fail.[5]

Patients with mild disease, introducing them to the hospital, may not be necessary, if there is no concern about quick worsening or an inability to quickly return to the hospital, but the quarantine to prevent virus transmission should be arranged. All patients taking care outside the hospitals should be educated to accomplish themselves properly according to the public health practices for home quarantine and further sent back to a selected COVID-19 hospital if they get worse.[14]

If care is to be delivered at home, an expert HCW, should conduct a valuation to confirm that the residential situation is appropriate for giving care; therefore HCW need to well evaluate whether the patient and the family are able to follow the precautions that are suggested as part of home care quarantine (e.g., hand sanitization, respiratory sterility, environmental hygiene, restrictions on movement around or from the home) and shall be able to report safety concerns (e.g., accidental consumption of and fire dangers related to the consuming alcohol-based hand wipes.[14,15]
- The patient and other house members should be provided with continuing support and instruction, and monitoring should continue for the period of house care. Home members should follow the following recommendations.[14] Firstly, the patient shall be put in a well-ventilated single room (Open the windows frequently).
- Restrict the movement of the patient in the home and to reduce shared space like the bathroom and kitchen).
- Family members should remain in a different room or, keep a remoteness of at least 1 m from the patient.
- Allow only one caregiver to provide care to the patient. Ideally, one who is in good healthiness and has no underlying long-lasting or immune-compromising circumstances.
- While cleaning hands with soap and water, it is desirable to use throwaway paper wipes to dry hands.
- Caregivers must use a medical mask and shall protect their mouth and nose during taking care of the patient in the same room, and the patient should always be provided a medical mask to wear as much as possible.[15]

Immediate implementation of suitable IPC (infection prevention and control) measures

IPC is a critical and essential part of the clinical control of patients and WHO guidance is existing. To accomplish the peak level of success in the response to the COVID-19, occurrence using the policies and practices recommended, an IPC program with a committed and qualified team, or at least an IPC important point should be in place and reinforced by the national and facility senior organization. In countries where IPC is incomplete or inexistent, it is essential to begin by confirming that at least minimum necessities for IPC are in place

Table 2. **Clinical syndromes associated with COVID-19 infections the child.**

SARI	**An ARI with a history of fever or measured temperature ≥38°C and cough start within the last ten days and necessitating hospitalization.**
Uncomplicated illness	• Patients with uncomplicated upper respiratory tract viral infection may have non-specific symptoms such as fever, cough, sore throat, nasal congestion, malaise, and headache. The elderly and immune-suppressed may present with atypical symptoms. These patients do not have any signs of dehydration, sepsis, or shortness of breath.
Mild pneumonia	• Patient with pneumonia and no signs of severe pneumonia. A child with non-severe pneumonia has cough or difficulty in breathing/fast breathing: (fast breathing - in breaths/min).
Severe pneumonia	• Adolescent or adult: fever or suspected respiratory infection, plus one of the following; respiratory rate >30 breaths/min, severe respiratory distress, SpO2 <90% on room air. • The child with cough or difficulty in breathing, plus at least one of the following: • Central cyanosis or SpO2 <90%; severe respiratory distress (e.g. grunting, chest indrawing); signs of pneumonia with any of the following danger signs: • Inability to breastfeed or drink, lethargy or unconsciousness, or convulsions. Other signs of pneumonia may be present: chest in drawing, fast breathing (in breaths/min): <2 month's ≥60; 2–11 months ≥50; 1–5 years ≥40. The diagnosis is clinical; chest imaging can exclude complications.
Acute Respiratory Distress Syndrome	• Onset: new or worsening respiratory symptoms within one week of known clinical insult. • Chest imaging (radiograph, CT scan, or lung ultrasound): bilateral opacities, not fully explained by effusions, lobar or lung collapse, or nodules. • Origin of edema: respiratory failure not fully explained by cardiac failure or fluid overload. • Need objective assessment (e.g. echocardiography) to exclude hydrostatic cause of edema if no risk factor present. Oxygenation (adults): • Mild ARDS: 200 mmHg < PaO2/FiO2 ≤ 300 mmHg (with PEEP or CPAP ≥5 cm H2O, or non-ventilated) • Moderate ARDS: 100 mmHg < PaO2/FiO2 ≤200 mmHg with PEEP ≥5 cm H2O, or non-ventilated) • Severe ARDS: PaO2/FiO2 ≤ 100 mmHg with PEEP ≥5 cm H2O, or no ventilated) • When PaO2 is not available, SpO2/FiO2 ≤315 suggests ARDS (including in non-ventilated patients) Oxygenation (children; note OI = Oxygenation Index and OSI = Oxygenation Index using SpO2) • Bi-level NIV or CPAP ≥5 cm H2O via full face mask: PaO2/FiO2 ≤ 300 mmHg or SpO2/FiO2 ≤264 • Mild ARDS (invasively ventilated): 4 ≤ OI < 8 or 5 ≤ OSI < 7.5 • Moderate ARDS (invasively ventilated): 8 ≤ OI < 16 or 7.5 ≤ OSI < 12.3 • Severe ARDS (invasively ventilated): OI ≥ 16 or OSI ≥ 12.3

and to progressively move to the complete achievement of all necessities of the IPC central components according to local priorities.[3]

IPC approaches to stop or restrict spread in health care settings include the following:

1. Ensuring triage, initial recognition, and source control (quarantining patients with predicted COVID-19).
2. Applying standard precautions and protection rules for all patients.
3. Realizing empiric extra precautions (droplet and contact and, at any time appropriate, airborne precautions) for assumed cases of COVID-19.
4. Implementing administrative and organizational controls.
5. Using environmental and engineering panels.

1. Ensuring triage, initial recognition, and source control (quarantining patients with predicted COVID-19).[16]

Clinical triage involves a system for evaluating all patients at admittance, allowing for initial recognition of probable COVID-19 and instant quarantine of patients with assumed illness in a region isolated from other patients (source control).[17] To enable the initial identification of cases of predicted COVID-19, health-care facilities should:

- Inspire HCWs to have a high level of clinical doubt.
- Create a well-resourced triage location at the entrance to the facility, reinforced by skilled staff.
- Introduce the usage of screening surveys according to the rationalized case definition. Post signs in public regions prompting symptomatic patients to alert HCWs.
- Hand sanitation and respiratory hygiene are crucial preventive methods.[3]

2. Applying standard precautions and protection rules for all patients.

Standard precautions involve hand and respiratory sanitization, the use of suitable personal protective equipment (PPE) according to a risk evaluation, injection safety approaches, safe waste disposal, appropriate linens, environmental hygiene, and sterilization of patient-care apparatus. Respiratory hygiene measures include:

- Make sure that all patients shield their nose and mouth with a tissue or elbow when coughing or sneezing.
- Give a medical mask to patients with predicted COVID-19 while they are in waiting zones or cohorts housings.
- Achieve hand hygiene after interaction with respiratory discharges.

Hand hygiene approaches should be performed by HCW's prior to contact with a patient, before any hygienic or aseptic technique is achieved, after contact with body fluid, after touching a patient, and after contact with the patient's surroundings.

- Hand hygiene involves both washing hands with an alcohol-based hand wipe and cleaning them with soap and water.
- Alcohol-based hand wipes are favored if hands are not obviously dirty.

- Rinse hands with soap and water when they are obviously dirty.[16]

3. Realizing empiric extra precautions (droplet and contact and, at any time appropriate, airborne precautions) for assumed cases of COVID-19.

3.1 Contact and droplet precautions:

Droplet and contact precautions avoid direct or indirect spread from interaction with polluted surfaces or apparatus (contact with contaminated oxygen tubes). Put PPE (triple layer medical mask, eye protection, gloves, and robe) when arriving room and get rid of PPE when leaving.

If probable, use either throwaway or dedicated apparatus (e.g., stethoscopes, blood pressure cuffs, and thermometers). If the apparatus needs to be mutual among patients, sterilize, and disinfect after each patient use. Make sure that HCWs abstain from dabbing their eyes, nose, and mouth with possibly polluted gloved or ungloved hands. Avert contaminating environmental planes that are not directly connected to patient care (e.g., doorknobs and light bottoms). Make sure that room ventilation is enough. Avert movement of patients or transport.

3.2 Airborne precautions:

Some aerosol-generating actions, such as tracheal intubation, non-invasive ventilation, tracheotomy, cardiopulmonary resuscitation, manual ventilation prior to the intubation, and bronchoscopy, have been linked to an elevated risk of spread of coronaviruses.

- Make sure that HCWs performing aerosol-generating actions put PPE. At any time possible, use sufficiently ventilated single places when performing aerosol-generating actions, meaning negative pressure rooms with a minimum of twelve air alterations per hour or at least 160 L/s/patient in facilities with normal ventilation.
- Evade the existence of needless individuals in the room. Care for the patient in a similar kind of room after automatic ventilation commences.
- Restrict the number of persons existing in the room to the absolute minimum essential for the patient's care and maintenance.[18]

4. Implementing administrative and organizational controls.

Organizational controls and policies for the prevention and control of transmission of COVID-19 within the health-care setting include: creating maintainable IPC infrastructures and activities, instructing patients caregivers, improving policies on the early recognition of acute respiratory infection possibly triggered by COVID-19 virus, confirming entrance to prompt laboratory testing for the identification of the etiologic agent, avoiding overcrowding, particularly in an emergency setting, providing devoted waiting zones for patients with symptoms, properly separating hospitalized patients; ensuring enough materials, and ensuring commitment to IPC strategies and procedures for all sides of health care.[16]

5. Using environmental and engineering panels.

These controls report the basic infrastructure of the health-care capability, and its purpose is to make sure that the ventilation in all areas in the health-care facility is adequate, as well as adequate environmental sanitization. In addition, a distance of at least 1 m would be kept between all patients.[18]

Both spatial detachment and enough ventilation can assist reduce the diffuse of many pathogens in the health-care setting. Guarantee that cleaning and disinfection measures are followed regularly and appropriately. Washing environmental surfaces with water and detergent and put on frequently used hospital disinfectants (like sodium hypochlorite) is effective and adequate. Accomplish laundry, food service implements, and medical discarded in agreement with harmless routine procedures and actions.[19]

Early supportive therapy and monitoring

A. Provide supplementary oxygen therapy instantly to patients with SARI and respiratory distress, hypoxemia, or shock. Start oxygen therapy at 5 L/min and titrate flow rates to achieve target SpO2 ≥90% in non-pregnant patients and SpO2 ≥ (92-95) % in pregnant women. Children with emergency signs (obstructed or lacking breathing, severe respiratory distress, central cyanosis, shock, coma, or seizures/convulsions) have to receive oxygen therapy while resuscitating them to target SpO2 ≥94%, then, the target SpO2 is ≥90%.

B. The most important equipment that should be found in patients caring rooms includes pulse oximeters, effective oxygen systems and throwaway, single-use, oxygen-delivering interfaces (nasal cannula, simple face mask, and mask with reservoir bag). Use interaction safety measures when holding contaminated oxygen interfaces of COVID–19 patients.[20]

C. Use conservative fluid controlling in patients with SARI when the shock is not evident. Patients with SARI should be treated carefully with IV fluids, because of violent fluid resuscitation may deteriorate oxygenation, particularly in situations where there is restricted accessibility of mechanical ventilation.[21]

D. Provide empiric antimicrobials to treat all expected microbes causing SARI. Offer antimicrobials within 1 h of primary patient assessment for patients with sepsis. Initial antibiotic treatment would be established based on the clinical diagnosis (community-acquired pneumonia, health-care-associated pneumonia, local epidemiology, and vulnerability data, and therapy procedures. Empirical treatment involves a neuraminidase inhibitor for the cure of influenza when there is local circulation or other risk factors, including transportation history or exposure to animal influenza viruses. Initial therapy has to be scale down on the basis of microbiology outcomes and clinical decisions.[22]

E. Systemic corticosteroids should not be given regularly for the treatment of viral pneumonia or acute respiratory distress syndrome (ARDS) except for clinical trials unless they are designated for another reason. This is because corticosteroids ordered to patients with SARS stated no survival assistance and probable harms (avascular necrosis, psychosis, diabetes, and delayed viral clearance). In addition, a greater risk of mortality and secondary infections with corticosteroids was established.[23]

F. Strictly observer patients with SARI for signs of clinical worsening, such as quickly progressive respiratory failure and sepsis, and use supportive care interventions straightaway.[20]

G. Recognize the patient's co-morbid circumstances to adjust the management of serious illness and appreciate the prognosis.[20]

Collection of specimens for laboratory diagnosis

Precise diagnosis is by specific molecular trials on respiratory samples (throat swab/nasopharyngeal swab/sputum/endotracheal aspirates and bronchoalveolar lavage). The virus may also be noticed in the stool and in severe cases, the blood. It is essential to remember that the multiplex PCR plates presently existing exclude the COVID-19. Commercial tests are also not accessible at present.

Additional laboratory examinations are frequently non-specific. The white cell count is generally normal or low. There may be lymphopenia; a lymphocyte count of less than 1000 has been related to the severe disease. The platelet count is commonly normal or slightly low. The CRP and ESR are usually high, but procalcitonin levels are frequently normal. A high procalcitonin level may point to a bacterial co-infection. The ALT/AST, prothrombin time, creatinine, D-dimer, CPK, and LDH may be raised and high levels are linked to severe disease.[24]

The chest X-ray (CXR) typically demonstrates bilateral infiltrates but may be normal in the early stages of infection. The CT is more sensitive and precise. CT imaging commonly indicates infiltrates, ground-glass opacities, and subsegmental consolidation. It is also irregular in asymptomatic patients or patients with no clinical suggestion of lower respiratory tract association. Actually, abnormal CT scans have been employed to identify COVID-19 in uncertain cases with the negative molecular diagnosis; many of these patients had positive molecular tests on duplication of testing.[25]

Fast gathering and testing of suitable samples from patients meeting the supposed case definition for COVID-19 is important for clinical management and outbreak control and need to be directed by a laboratory expert. Supposed cases should be checked for the virus with nucleic acid amplification tests (NAAT), like RT-PCR.

Safety procedure during specimen collection

Make sure that adequate standard operating procedures (SOPs) are in usage, and that team is skilled for correct specimen assembly, storage, packing, and transportation. All samples collected for laboratory examinations should be considered as possibly infectious and transmittable. Make sure that HCWs who gather samples comply strictly with infection prevention and control procedures.[26]

The specimen to be collected

At least, respiratory material should be sampled:

- Upper respiratory samplings: nasopharyngeal and or pharyngeal swab or wash in ambulatory patients.
- And/or lower respiratory samplings: sputum (if formed) and/or endotracheal aspirate or bronchoalveolar lavage in patients with more severe respiratory illness.

Further clinical samples may be collected as COVID-19 virus has been distinguished in blood and stool, as had the coronaviruses responsible for SARS and MERS. The interval and incidence of shedding of COVID-19 virus in stool and possibly in urine is unidentified. In the case of patients who are dead, consider post-mortem material as well as lung tissue. In living patients, combined serum (acute and convalescent) can be valuable to retrospectively define cases as serological analyses become existing.[27]

Packaging and shipment of clinical samples

Samples for virus recognition should reach the laboratory immediately after gathering. The right holding of specimens during shipping is critical. Specimens that can be transported rapidly to the laboratory can be put in storage and shipped at 2–8°C. If there is any suspected delay in specimens' transportation to the laboratory, the use of a viral transportation medium is powerfully suggested. Samples may be frozen to -20°C or ideally -70°C and transported on dry ice if additional delays are probable. It is essential to evade frequent freezing and melting of samples.[27]

Nucleic acid amplification tests (NAAT) for COVID-19 virus

Routinely validation of cases of COVID-19 is established on recognition of distinctive sequences of virus RNA by NAAT such as real-time reverse-transcription polymerase chain reaction (rRT-PCR) with approval by nucleic acid sequencing when essential. The viral genes directed until now contain the N, E, S, and RdRP genes. RNA extraction ought to be done in a bio-safety cabinet in a BSL-2 or the same facility. Heat treatment of specimens prior to RNA extraction is not suggested.[25]

In hospitalized patients with established COVID-19 infections, repeat URT samples would be gathered to prove viral clearance. The frequency of sample assembly will be influenced by the local conditions but should be completed at least every 2–4 days until there are two consecutive negative results (of URT samples) in a clinically improved patient at least 1 day.

Coronavirus statistics and charts

There are 2,395,636 confirmed cases and 164,565 deaths from the coronavirus COVID-19 outbreak as of April 19, 2020, 19:37 GMT. But, now there are more than 10,088,576, cases confirmed by the end of June 28, 2020 and more than 501,442, deaths. The greatest number of new cases and deaths of COVID-19 are now being reported in the USA, Brazil, Russia, Spain, the UK, Italy, Germany, France and this growing number of cases is due to the person-to-person transmission. As represented in Fig 1, countries cases distribution has been reported to be the highest in USA, Brazil, and Russia with, 25.74%, 13.04%, and 6.22%, respectively. This may contribute to the large population size as in USA, Russia, or the low treatment facilities as in Brazil, in contrast to the better approaches in the medical services which are used in the European countries which have shown a moderate distribution in UK, Italy, India, Peru, Spain, 3.08%, 2.38%, 5.25%, 2.74%, and 2.93%, respectively.

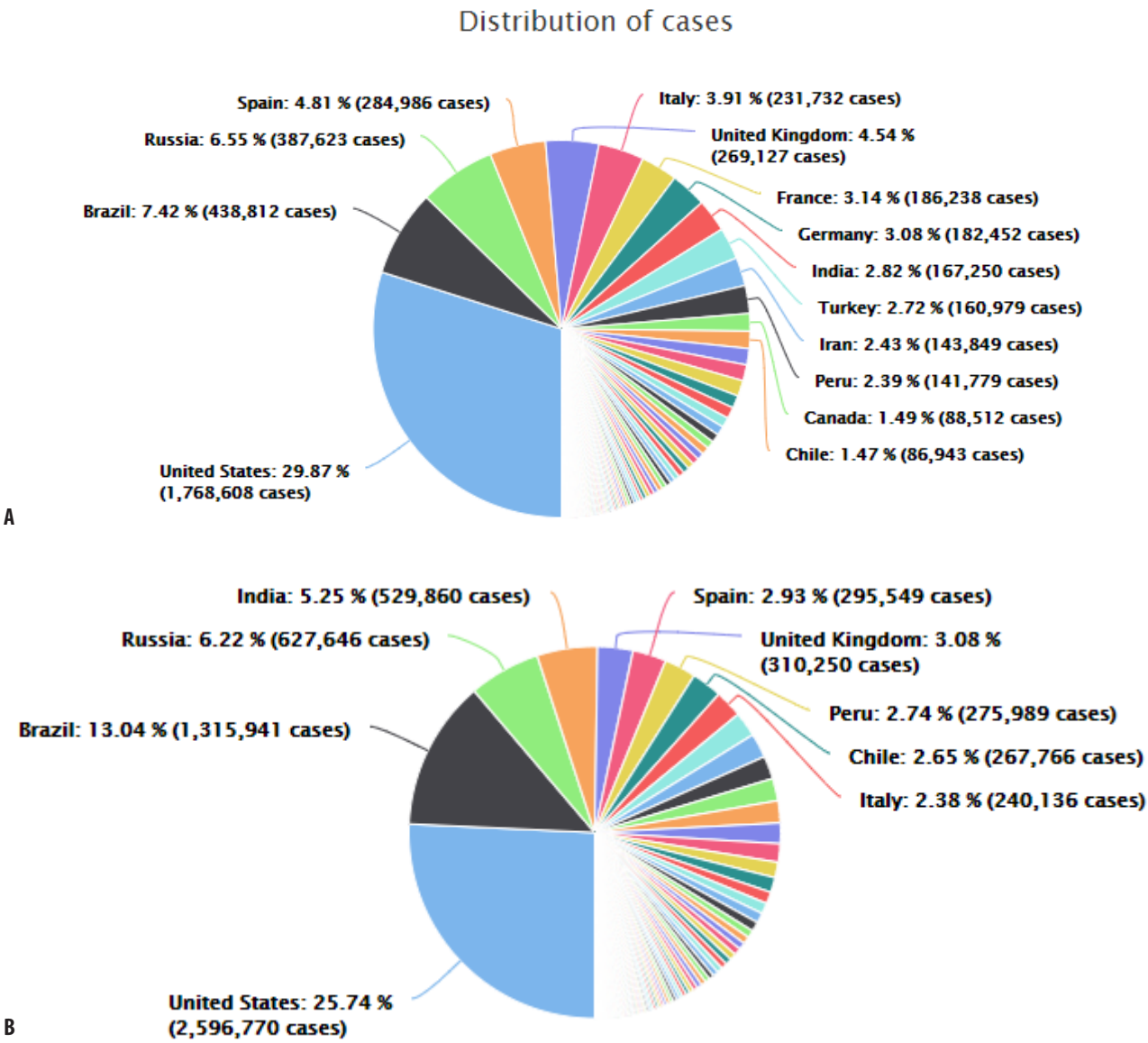

Fig. 1 **(A) Countries cases distribution (by end of May 2020), (B–A) Countries cases distribution (by June 28, 2020, https://www.worldometers.info/coronavirus/worldwide-graphs/)**

On April 3, the French Government reported 17,827 additional cases and 532 additional deaths from nursing homes that had not been reported previously. On April 2, it had reported 884 additional deaths. On February 12, China reported 51,152 additional new cases due to a change in how cases were diagnosed and reported (https://www.worldometers.info/coronavirus/worldwide-graphs/).

There are four main gaps between stated cases and real cases:

1. **Inadequate testing:** Countries that lack the systems or capacity to test appropriately.
2. **Yet to be stated cases:** People who have the virus but are either: yet to present with symptoms, yet to be tested, or had a test that revealed a false negative.
3. **Asymptomatic cases:** Approximations are that about half of all persons who get the virus will never present with symptoms.
4. **Purposely under-reported:** Some countries appear to be deliberately under-reporting cases.

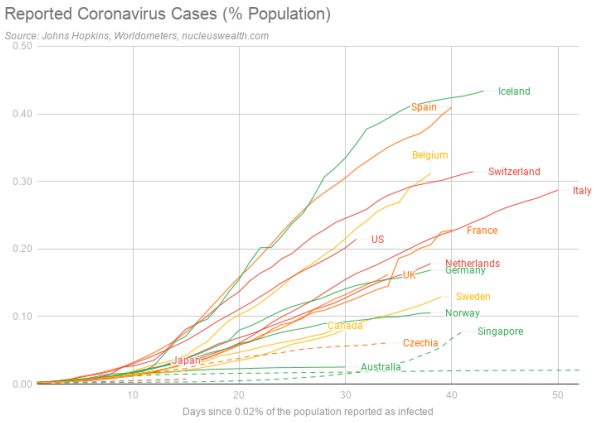

Fig. 2 **Reported coronavirus cases (% population).**

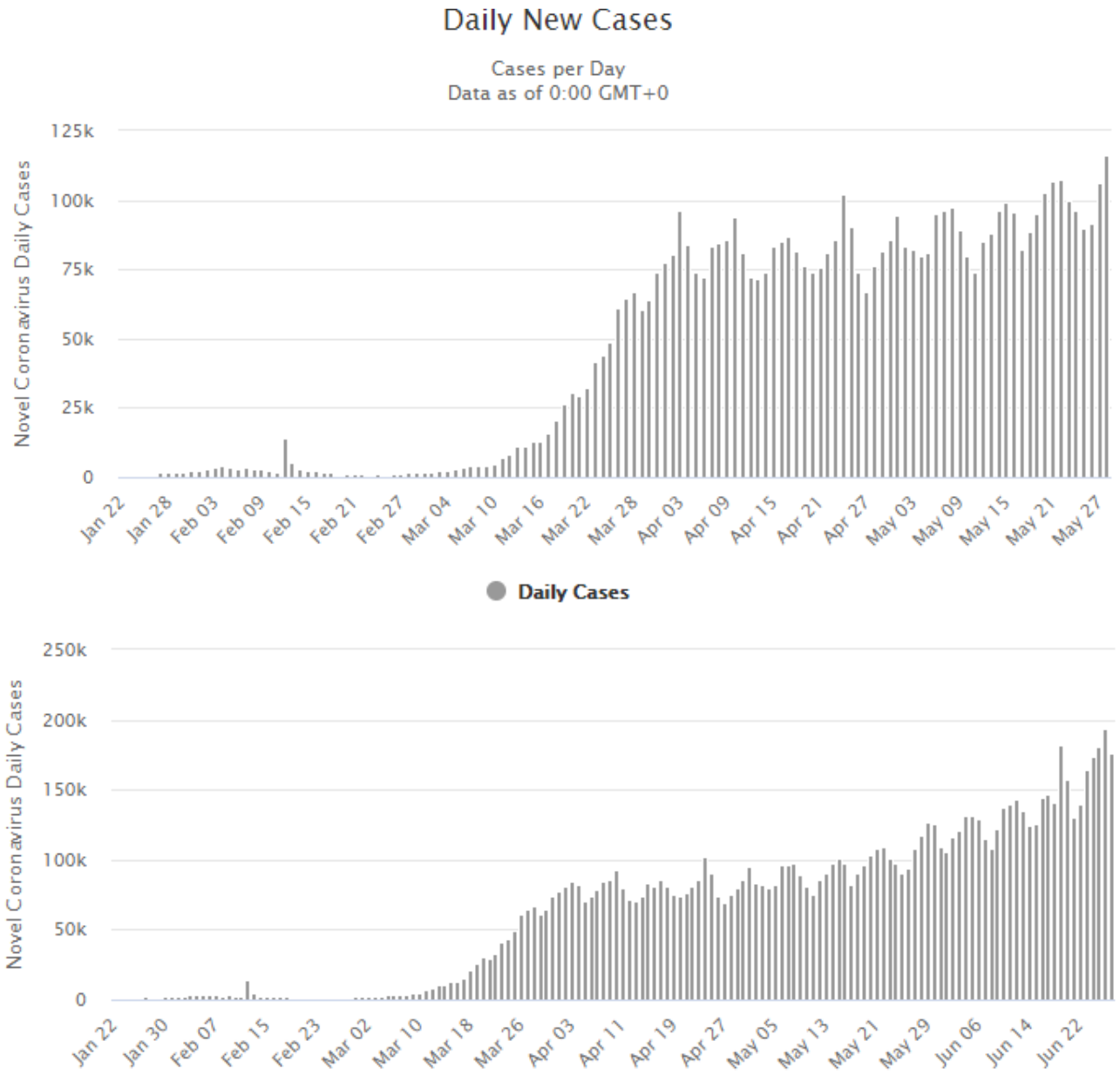

Fig. 2 **Daily cases (worldwide), https://www.worldometers.info/coronavirus/worldwide-graphs/.**

Among all cases

Hospitalization happened in 32% (48,755 of 152,375) of cases stated from 26 countries (median country detailed estimation, interquartile range (IQR), 28%, 14–63%). Severe illness (needing ICU or respiratory support) accounted for 2,859 of 120,788 (2.4%) of cases informed from 16 countries (median, IQR: 1.4%, 0–33%).

Among hospitalized cases

The severe illness was stated in 9.2% (3,567 of 38,960) of hospitalized cases from 19 countries (median, IQR: 15%, 3.8–35%). The death happened in 1,005 of 9,368 (11%) hospitalized cases from 21 countries (median, IQR: 3.9%, 0–13%). The following table summarizes the number of cases, deaths and recovery for some countries as on May 29, 2020 (Table 3), https://www.statista.com/page/covid-19-coronavirus.

Management of mild cases of patients with confirmed COVID-19 disease

Mild cases are asymptomatic patients or patients with mild fever (37.5), cough, cold symptoms, nasal congestion, malaise, and without dyspnea. Approximately, most patients have mild or no symptoms. The most important step in care is the isolation of the patients to prevent transmission of the virus to other relatives or health-care providers.[28]

Mild cases need supportive care and symptomatic treatment with antipyretic agents, if needed only, paracetamol is the first line and NSAIDs have caution in use hydration and nutrition supplements should receive and ensure adequate calories intake. Frequent cough and fever monitoring. The organ function should routinely control, and any secondary infection should be prevented. All management is in their houses unless there are severe symptoms. If there is any development in the disease patient must refer to the health-care center.[29]

as of May 29, 5:30 GMT	Total infections	Active infections	Recoveries	Deaths
Total (worldwide)	5,909,081	2,964,912	2,582,078	362,091
USA	1,768,461	1,166,406	498,725	103,330
Brazil	438,812	218,867	193,181	26,764
Russia	379,051	223,916	150,993	4,142
Spain	284,986	60,909	196,958	27,119
United Kingdom	269,127	N/A	N/A	37,837
Italy	231,732	47,986	150,604	33,142
France	186,238	90,385	67,191	28,662
Germany	182,452	10,682	163,200	8,570
India	165,799	89,982	71,106	4,711
Turkey	160,979	32,149	124,369	4,461

Management of severe cases of patients with confirmed COVID-19 disease

A: Oxygen therapy

Patients develop severe symptoms that have respiratory distress (less than 30 breath/min), oxygen saturation less than 90%, cyanosis, and shock must receive oxygen therapy by including nasal catheter and mask oxygenation and nasal high-flow oxygen therapy. If possible, inhalation of mixed hydrogen and oxygen (H_2/O_2: 66.6%/33.3%) can be applied to target more than 91% of oxygen saturation in non-pregnant adults and 92-95% to pregnant ones at room air.[30]

The nasal cannula is preferred for children with respiratory distress because it is better to tolerate. High flow nasal catheter or non-invasive mechanical ventilation is used when the respiratory distress does not relieve after standard oxygen therapy. High flow nasal catheters consider safer than non-invasive ventilation because many scientists suggest that it may associate with the nosocomial transmission of the disease. About one- or two-third of critically ill-patients need them. If the patient doesn't improve in time nearly 1–2 h invasive mechanical ventilation should be considered. The invasive mechanical ventilation used to avoid ventilator-induced lung injury while facilitating gas exchange via lung-protective ventilation.[31]

Patients with severe symptoms should be equipped with pulse oximeters, functioning oxygen systems and disposable, single-use, oxygen-delivering interfaces (nasal cannula, nasal prongs, simple face mask, and mask with reservoir bag), and should have regularly mentoring of vital sign.[5]

In the case series of 99 hospitalized patients with COVID-19 infection from Wuhan, oxygen was given to 76%, non-invasive ventilation in 13%, mechanical ventilation in 4%, extracorporeal membrane oxygenation (ECMO) in 3%.[5]

B: Therapeutic agents

B.1: Chloroquine and hydroxychloroquine

Chloroquine and its analogs are employed for the treatment and prevention of malaria in the 1900s. In addition to that, they possess immunomodulatory effects for the treatment of autoimmune diseases as systemic lupus erythematosus and rheumatoid arthritis. And they have antiviral properties especially for viruses that induced inflammation like Ebola, HIV, and SARS.[32]

These agents are non-protonated, when they are introduced intracellularly they become protonated and increase the pH of the corresponding cell. The pH changes inhibit viral infusion with the cell membrane of the host. They can also inhibit nucleic acid replication and appear to interfere with the terminal glycosylation of ACE2 receptor expression which shall prevent SARS-CoV-2 receptor binding and subsequent spread of infection.[33]

Studies have shown that chloroquine has a potent cytotoxic response with 99% inhibition of viral replication; moreover, *in-vivo* models show high inhibition of viral spread before viral exposure in which it concludes that they may be used as a prophylactic agent. The working group is expressed against the possible use of chloroquine, hydroxychloroquine in prophylaxis for COVID-19. At present, there is no evidence of the efficacy of this drug in the prevention of disease COVID-19. Savarino et al hypothesize that CQ might block the production of pro-inflammatory cytokines (such as interleukin-6), thereby blocking the pathway that subsequently leads to ARDS. Based on this finding, the experts and organizers of clinical trials suggested that chloroquine is a promising antiviral agent against SARS-CoV-2. Hydroxychloroquine showed a safety profile and three times more potent than chloroquine in cytotoxic response so less dose of hydroxychloroquine is used.[24]

Taking also into account that therapy would be likely required mostly in older patients and/or in case of severe disease (at least for the moment). This study, which has meanwhile been published, suggests that SARS-CoV-2 positivity in nasopharyngeal secretions (measured by RT-PCR) is significantly decreased at day 6 after inclusion (i.e. day 10 after symptom onset) in hydroxychloroquine-treated COVID-19 patients (n=26) versus patients who received supportive care only (n=16 external controls). However, the study has a limitation of small size and the non-homogeneous group they consider as the first line for severely ill patients. The same line

is not recommended for out-patients because there is no sufficient study for efficacy and cost-benefits.[34]

Current *in-vitro* pharmacokinetic models suggests a loading dose of hydroxychloroquine 400 mg orally twice daily on day 1, followed by 200 mg orally twice daily for 4 days. The panel recommends the use of the drug at a dose of 500 mg BID for 10 days. Alternatively, you can use if it were not available chloroquine, hydroxychloroquine 200 mg BID. These agents have been mostly tolerated with patients but it has gastrointestinal adverse effect and toxicity cause neuropathy, retinopathy and cardiomyopathy but that happened with a long-term, not in short-term. Concurrent administration of QTc prolonging agents and strong 2D6 inhibitors (chloroquine only) should be avoided to minimize cardiac adverse effects. Although the manufacturer's labeling of chloroquine and hydroxychloroquine caution against their use in patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency, there are limited data to support this risk and no incidence of hemolytic anemia has been seen in patients with G6PD in 30 years of drug exposure.[35]

B.2: Remdesivir

Remdesivir is pro-drug which contains 1'-cyano-substituted adenosine nucleotide analog, in which its action is to metabolize the cell and tissue, so in order to activate the nucleoside triphosphate (GS-443902) which shall inhibit the viral RNA-dependent RNA polymerases in the viral infectious cycle cascade. The second action is adenosine analog which may involve lethal mutagenesis and chain termination. Initially, it is developed for the treatment of Ebola hemorrhagic fever, but it has no approval until now for any indications.[36]

Nucleotide analogs use for RNA viral for inhibition of viral replication by suppression of polymerases enzyme; however, many viruses have resistance to these agents which result in exo-ribonuclease proofreading and removal. Remdesivir has the potential to avoid this proofreading. *In-vitro* study showed its activity in human lung epithelial cells against Coronaviruses. In China, two phases 3 randomized, open-label trials, NCT04292899 and NCT04292730, initiated by the manufacturer (Gilead) to evaluate the safety and antiviral activity of 5- and 10-day regimens of Remdesivir, in conjunction with the standard of care in patients with severe and moderate COVID-19, which are estimated to finalize patient recruitment by May 2020. In the United States, Remdesivir has been used for 4–10 days until the respiratory symptoms improve.[37]

Remdesivir is used as 200 mg IV loading dose within 30 min, then 100mg OD for 2–10 days. Some adverse effects appear while using Remdesivir as nausea, vomiting, rectal bleeding, and elevated aminotransferase level. However, it is still not clear that those effects are generally from the disease or drug itself. No clinical study to elucidate the usage of the drug for pregnant women and drug–drug interaction is still not reported.[38]

B.3: Lopinavir/Ritonavir

Lopinavir is an aspartic acid protease inhibitor. Proteases are essential enzymes for replication and maturation of viruses, so Lopinavir inhibits the spread of the virus in the host cell. Ritonavir combined to boots half live of Lopinavir by inhibition of CYP450. The drug has been approved for use in the treatment of the HIV virus. A recent study showed that Lopinavir/Ritonavir has an effect on the inhibition of 3-chymotrypsin like protease which found to be a novel Coronavirus.[39]

In a recent study, Bin Cao et al., randomized a total of 199 patients with laboratory-confirmed SARSCoV-2 infection that 99 patients treated with Lopinavir/ritonavir and 100 patients treated with standard care. The Lopinavir/Ritonavir was not associated with any development and treatment effects subsequently, the number of death after 28 days was the same in the two groups, so this elucidates that there is no benefit associated with its usage in severely ill patients.[40]

However, there are still trials suggest that Lopinavir/Ritonavir have possible benefit in patients who were treated before 12 days of symptom. The available doses are 400/100 mg or 200/100 mg. if Lopinavir/Ritonavir is used as an adjunctive agent for COVID-19, a dose of 400 mg/100 mg by mouth twice daily for 14 days is recommended. These agents still require the second line for COVID-19 treatment in the case when chloroquine is contraindicated.[39]

The usage of Lopinavir/Ritonavir is associated with gastrointestinal toxicities, diarrhea, and vomiting; however, administering it with food may ameliorate these effects. According to multiple collected data, Lopinavir/Ritonavir is not associated with teratogenicity effects in pregnant women with HIV, so it can be used if there isn't a present of any contraindication.[39]

B.4: Ribavirin

Ribavirin is a prodrug of purine nucleoside analog, which its derivative in the liver to closely mimic the purine analog guanosine which incorporates with RNA. The structural elements prohibit the subsequent addition of nucleoside analogs, effectively halting the synthesis of RNA. It is used for hepatitis C, B, and respiratory viruses.[41] In 126 cases treated with ribavirin, hemolysis and anemia occurred in up to 76% and 49% of cases, respectively; however, no effect to use Ribavirin as monotherapy, but potential activity when combined with other antiviral agents such as LPV/RTV or chloroquine analogs. Oral ribavirin has been dosed as a 4-g loading dose followed by 1.2 g every 8 h in two small studies for SARS. In the management of COVID-19, data are limited to ongoing studies using a dosing strategy of 400 mg by mouth twice daily for 14 days as a part of a combination regimen.[42]

Ribavirin needs special precaution while usage, because it is associated with hemolytic anemia, especially after taking a high dose (1–2 g), which is needed for Coronaviruses treatment. Ribavirin is a teratogen, with a significant potential for embryonic toxicity and is usually contraindicated in women who are pregnant and in male partners of those pregnant women. Ribavirin in combination with other immunosuppressive therapies, particularly azathioprine or IFN can lead to severe pancytopenia.[41]

C. Immune modulating agents

C.1: Interferon-alpha

Interferon is an endogenous protein released by the host cell in action of inflammation and infection. It stimulates the immune response against viral replication. It is upregulated in many viral infections, such as hepatitis. This non-specific immune-modulatory response is the attractive reason to use it in COVID-19 treatment. When interferon used for SARS, it has an action prior to exposure of infection via the inhibition of the virus replication. However, still there is no approved action after viruses' exposure.[43]

In-vivo studies have yet to be able to replicate the same benefits, with some studies showing no influence on the disease

course for MERS, while others suggest a small improvement in survival at 14 days but not 28 days when used in combination with ribavirin. Due to the lack of established human data with IFNs for COVID-19, this therapy should only be considered for COVID-19 as a part of a clinical trial. There is no established dosing regimen for IFN in the treatment of COVID-19. The only available data used for MERS treatment was via using a dose of 180 μg per week for 2 weeks.[43]

C.2: Tocilizumab

Tocilizumab is a humanized anti-interleukin 6 monoclonal antibody for the treatment of rheumatoid arthritis. It inhibits the interleukin 6 signaling pathway and competes with interleukin 6 binding sites on the cell membrane, so it inhibits the inflammation pathway. It is hypothesized that it works against cytokine storm with raised ferritin and interleukin-6 levels due to SARS-CoV-2. Recently published data from Wuhan indicates that tocilizumab added to Lopinavir, methylprednisolone, and oxygen therapy in 20 patients with severe COVID-19 resulted in rapid reductions in fever in all patients, improvement in oxygenation for 75%, and facilitated discharged from the hospital in 95% of patients.[44]

Tocilizumab for most indications is weight-based with a maximum dose of 800 mg. The dosing of tocilizumab for COVID-19 is still not well established. When used in a case series of patients with COVID-19, a one-time dose of intravenous tocilizumab 400 mg was administered. However, until now, there are no peer study approved uses of Tocilizumab.[45]

International protocols for COVID-19 treatment guidelines

A: Italian protocol

Table 4. **Italian Society of Infectious and Tropical Diseases section therapeutics protocol.**

Clinical observation	Recommendation
Patient positive for COVI-19 asymptomatic or mild symptoms: (fever (>37.5° C), cough, cold symptoms without dyspnea), age <70 years with no risk factors (COPD, diabetes and heart disease) and RX normal chest	Clinical observation, supportive care
Patient positive for COVI-19 with mild respiratory symptoms but age >70 years and/or with risk factors (COPD, diabetes and heart disease) or symptomatic or mild symptoms (fever (>37.5° C), cough, dyspnea on mild to moderate) and chest radiography with pneumonia framework	Lopinavir/Ritonavir 200/50 mg cps, 2 x 2 / day (800 mg darunavir alternatively 1 cp / day + ritonavir 100 mg 1 cp / day or darunavir / cobicistat 1 cp 800/150 mg / day) 500 mg + chloroquine, 1 x 2 / day or hydroxychloroquinecp 200 mg, 1 x 2 / day. Duration of therapy: 5 to 20 days, with timing to be determined according to clinical evolution.
Case of need for oxygen therapy or rapid clinical deterioration (see "supportive measures" and COVID respiratory severity scale)	Remdesivir requests for compassionate use. At the time of its availability suspend LPV / RTV (or DRV / b) and continue with:
	Remdesivir vials 150 mg period: 1 day 200 mg IV 30 minutes then 100 mg IV / day for another 9 days in combination with chloroquine 500 mg, 1 x 2 Day or hydroxychloroquine 200 mg, 1 x 2 / day (duration of therapy: from 5 to 20 days, with timing to be determined according to clinical evolution). If the patient has a BCRSS score. Evaluate 2: dexamethasone 20 mg/day for 5 days and then 10 mg/day for 5 days (as indicated by intensivistica) and / or tocilizumab
Positive Patient COVID for-19 with the picture of severe pneumonia, ARDS or global respiratory insufficiency, hemodynamic failure, need for mechanical ventilation (invasive or not)	Remdesivir 1 days 200 mg iv as loading dose, then 100 mg / day (days 2-10) + chloroquine 500 mg, 1 x 2 / day or hydroxychloroquine 200 mg x 2 via SNG (duration of therapy: from 5 to 20 days, with timing to be determined according to clinical evolution).
Patients ARDS: after 24 hours from the diagnosis of ARDS.	Dexamethasone 20 mg / day for 5 days and then 10 mg / day for 5 days (as indicated by intensivistica) and / or tocilizumab.

B. Belgian protocol

Table 5. **Belgian recommendation for patients with COVID-19.[46]**

Clinical observation	Recommendation
Suspicion of COVID-19 (Mild-to-moderate symptoms (no dyspnea), No risk group	Symptomatic treatment Use paracetamol in first-line
Suspicion of COVID-19. Mild-to-moderate symptoms (no dyspnea). Risk group or Suspicion of COVID-19 and alarming symptoms (dyspnea)	Case by case discussion, if possible with a communicable disease Specialist, to initiate an empirical antiviral therapy, supported the potential delay to get results (antiviral therapy is anticipated to be more efficient if started early within the course of the disease), or On other considerations (high risk of secondary complications).
Confirmed COVID-19. Mild-to moderate disease (no O2 requirement/no evidence of pneumonia)	Consider start hydroxychloroquine (Plaquenil®) IF NO CONTRAINDICATION • 400 mg at suspicion/diagnosis; • 400 mg 12 h later • Followed by 200 mg BID up to Day 5 If no hydroxychloroquine available, consider chloroquine base 600 mg (10mg/kg) at diagnosis and 300mg (5 mg/kg) 12 h later, followed by 300 mg (5 mg/kg) BID up to Day 5 or chloroquine phosphate 1000 mg at diagnosis and 500mg 12 h later, followed by 300mg BID up to day 5.

Confirmed COVID-19 Severe disease ≥1 of the following: Respiratory rate ≥30/min (adults), ≥40/min (children <5), Blood oxygen saturation ≤93%, PaO2/FiO2 ratio 50% of the lung field within 24-48 hours	Start hydroxychloroquine (Plaquenil®) IF NO CONTRAINDICATION • 400 mg at diagnosis; • 400 mg 12 h later • Followed by 200 mg BID up to Day 5. Consider Lopinavir/ritonavir 400/100 mg (= 2 tablets of 200/50 mg) BID for 14 days) as second choice ONLY if hydroxychloroquine/ chloroquine ne contra-indicated and provided it can be administered within 12 days after symptoms onset
Confirmed COVID-19 Critical disease ≥ 1 of the following: Acute Respiratory Distress Syndrome, Sepsis, Altered consciousness, and Multi-organ failure	Remdesivir (compassionate use) • 200 mg loading dose (IV, within 30 min) • 100 mg OD for 2 to 10 days If Remdesivir unavailable: Consider (hydroxy)chloroquine, crushed in the nasogastric tube, at the same dosage and monitoring as above; replace with Remdesivir if it becomes available Tocilizumab and other interleukins (6 or 1) blockers: Some Chinese, Italian and (very limited) Belgian clinical experience (unpublished) suggest a favorable effect in the most critical patients

Management of critical illness and COVID-19: Septic shock

Doctors notice a septic shock in some adults when infected with COVID-19, the treatment goal is to maintain mean arterial pressure (MAP) ≥ 65 mmHg, lactate ≥ 2 mmol/L. In absence of hypovolemia, the child will suffer from a septic shock with hypotension when (systolic blood pressure [SBP] < 5th centile or > 2 SD below normal for age) or suffers from two or more of the following: altered mental state; bradycardia or tachycardia (HR < 90 bpm or > 160 bpm in infants and HR < 70 bpm or > 150 bpm in children); prolonged capillary refill (> 2 sec) or feeble pulses; tachypnea; mottled or cold skin or petechial or purpuric rash; increased lactate; oliguria; hyperthermia or hypothermia. When lactate measurement isn't available blood pressure (i.e. MAP) and clinical signs of perfusion can be used to define shock.

Strategies for the resuscitation of adult and pediatric patients with septic shock include conservative fluid regimens, the crystalloid fluid which include normal saline and Ringer's lactate which is given as bolus infusion, hypotonic crystalloids, starches, or gelatins should not be used for resuscitation. Starches are associated with an increased risk of death and acute kidney injury. Gelatins are more expensive than crystalloids. Hypotonic solutions are less effective than isotonic at increasing intravascular volume. Treating sepsis also suggests the use of albumin when patients require substantial amounts of crystalloids, but this recommendation is based on low-quality evidence.

In adults with septic shock 250–500 mL crystalloid fluid which include normal saline and Ringer's lactate is given as rapid bolus in the first 15–30 min,[22] in children10–20 mL/kg crystalloid fluid is given as a bolus in the first 30–60 min, check for signs of fluid overload after each bolus.[47] Reduce or discontinue fluid administration if there is evidence of no response by the patient to fluid loading or if signs of volume overload appear on the patient (e.g., jugular venous distension, crackles on lung auscultation, pulmonary edema on imaging, or hepatomegaly in children), especially in patients with hypoxemic respiratory failure.

Based on clinical response and improvement of perfusion targets additional fluid boluses may be given (250–500 mL in adults or 10–20 mL/kg in children). The perfusion targets include MAP (>65 mmHg or age-appropriate targets in children), urine output (>0.5 mL/kg/h in adults, 1 mL/kg/h in children), and improvement of skin mottling and extremity perfusion, capillary refill, heart rate, level of consciousness, and lactate. Notice indices for volume responsiveness to fluid administration. These indices include passive leg raises, fluid challenges with serial stroke volume measurements, or variations in systolic pressure, pulse pressure, inferior vena cava size, or stroke volume in response to changes in intrathoracic pressure during mechanical ventilation.[22]

In pregnant women with sepsis and or septic shock, they may need to be placed in the lateral decubitus position to off-load the inferior vena cava to reduce the hypotension.[48] Management of septic shock in adults includes administration of vasopressors, in case if fluid administration does not restore adequate perfusion. In adults, norepinephrine is the first-line agent; epinephrine or vasopressin are preferred as the second line over dopamine, if patients didn't respond to usual doses of norepinephrine consider adding vasopressin rather than further titrating norepinephrine. In children, epinephrine is considered the first-line agent, and norepinephrine may be added if necessary. The initial blood pressure target is around 65 mmHg.[49] If signs of septic shock persist despite administration of fluids and vasopressors, the patient shall be given an inotrope agent such as dobutamine rather than further titrating norepinephrine.

Corticosteroids are recommended for patients with sepsis in whom adequate fluids and vasopressor therapy didn't restore hemodynamic stability. In those cases, you should balance the potential small reduction in mortality with the prolonged shedding of Coronavirus.

Adjunctive therapies for COVID-19: corticosteroids

Systemic corticosteroids are indicated as adjunctive therapies for COVID-19, in the case of asthma exacerbation or COPD and septic shock, otherwise, it should be avoided due to the lack of effectiveness and possible harm including avascular necrosis, psychosis, diabetes, and delayed viral clearance, in addition to, higher risk of mortality and secondary infections.[23] When using corticosteroids, it is mandatory to monitor and treat hyperglycemia, hypernatremia, and hypokalemia. When stopping corticosteroids taper down the dose, and monitor the recurrence of inflammation and the signs of adrenal insufficiency.[50]

Antenatal corticosteroid therapies are recommended for pregnant women at risk of preterm birth from 24 to 34 weeks of gestation when there is no clinical evidence of maternal infection. However, when a woman presents with mild COVID-19, the benefit of antenatal corticosteroid might outweigh the risks of potential harm to the mother.

Caring for pregnant women with COVID-19

Due to limited data, there is no evidence suggesting that pregnant are at higher risk of severe illness or fetal compromise. Mother-to-child transmission is still not approved. Samples taken from amniotic fluid, cord blood, vaginal discharge, neonatal throat swabs, or breast milk were negative. Pregnant women in the third trimester especially those who develop pneumonia may suffer from premature rupture of membranes, fetal distress, and preterm birth, preeclampsia, and cesarean delivery for fetal distress. WHO recommends that the cesarean section should be done only when medically justified.[51,52]

Emergency delivery and pregnancy termination decisions are based on many factors such as gestational age, the severity of the maternal condition, and fetal viability and well-being.

Neuraxial anesthetic advantages in laboring women providing good analgesia reduce cardiopulmonary stress from pain and anxiety in emergency cesarean by which it limits the need for general anesthesia. The use of nitrous oxide for labor analgesia should be avoided, because of insufficient data about cleaning, filtering, and potential aerosolization of nitrous oxide systems.

The use of magnesium sulfate for maternal seizure prophylaxis or neonatal neuroprotection may further depress respiration. Consultation with maternal–fetal medicine and pulmonary/critical care specialists is advised. The use of interventions such as a birth ball or peanut ball should be limited because it can increase the risk of infection. Intrapartum oxygen has no proven fetal resuscitation benefit, so it should be abandoned.

At delivery of patients COVID-19, institutions have been chosen to prohibit delayed cord clamping in term infants to minimize newborn exposure to the virus.

Use acetaminophen to relieve postpartum pain if possible, as NSAIDs are needed to use the lowest effective dose.

Caring for infants and mothers with COVID-19: IPC and breastfeeding

No virus was found in the breast milk of six infected patients.[51] However, close contact during breastfeeding could transmit droplets to the baby. Breastfeeding protects against morbidity in the post-neonatal as it is a passive source of antibodies and other anti-infective factors. Therefore, standard infant feeding guidelines should be followed with appropriate precautions for IPC. The earlier initiation of breastfeeding results in greater benefits, because of the dose–response effect.

If mother and baby separation have been implemented because the mother is too unwell to breastfeed or express breast milk, the infant is fed expressed breast milk by another healthy caregiver who follows hygiene precautions and use strict hand washing before pumping and wear a mask during pumping, the pumping equipment should be cleaned by a healthy person. If feeding by a healthy caregiver is not possible, mothers with confirmed COVID-19 should take precautions to prevent transmission of the virus to the infant during breastfeeding such as hand hygiene, use of a face mask, clean and disinfect surfaces which the symptomatic mother has been in contact. Due to the high prevalence of mental disorders among women in the postpartum period more widely interventions should be implemented to these women.[51]

Caring for older persons with COVID-19

COVID-19 affects the global population in drastic ways, older people face a greater risk of developing a severe illness because of underlying health conditions and many physiological changes that come with age which shall lead to declines in intrinsic capacity, manifested as the following malnutrition, cognitive decline, depressive symptoms, and potential underlying health conditions.[7] Early detection of inappropriate medication prescriptions is recommended to prevent adverse effects of drug or potential drug interactions with COVID-19 treatment.

Clinical research and specific anti-COVID-19 treatments

Many clinical trials are testing various potential antivirals, until now there no current evidence to recommend any specific anti-COVID-19 treatment. Collecting clinical data of all hospitalized patients is important to improve our understanding of the natural history of the disease. Investigational anti-COVID-19 therapeutics should be used only in approved, randomized, controlled trials.

Importantly, studies give proof that shows the transmission of this virus to human-to-human, along with many exported instances across the world. The geriatric population and people who are under some diseases are at risk of infection of this virus and susceptible to serious outcomes, which can be associated with acute breathing distress syndrome (ADRS).

The are several limitations such as: the virus spreads very fast, thus the actual and accurate causes and effective treatment of COVID-19 are still unknown or unavailable and the number of active cases of the infection is rising every day. However, the information about the disease including the number of cases and death are changing every day. The global impact of this new pandemic is yet uncertain. The numbers are possibly an underestimate of the infected and dead due to limitations of surveillance and testing. Though the SARS-CoV-2 originated from bats, the intermediary animal through which it crossed over to humans is uncertain. Pangolins and snakes are the current suspects.

Conclusions

The pandemic by COVID-19 is a very dangerous issue affecting people worldwide. Still this pandemic is ongoing and no suitable treatments for the patients arise on the horizon. Since the disease is a viral infection and viruses are known to undergo different antigenic shifting and antigenic drifting which still shows a problematic cause of importance toward better approaches in diagnosis and treatment, in addition to some comparative studies among different populations. Since as represented and shown that many coronaviruses dead people were distributed in Iran and Italy, therefore, this may arise a further question whether the population genetic or the immune system traits and nutritional status might contribute to this pathogenesis. Hence, here we provide review and some direct insights, and further directions on the situation and large picture of SARS-CoV in terms of health pandemic status. Moreover, the review reveals the pathophysiology of the disease and the major symptoms in those infected patients

among different age groups. Studies and investigations on the therapeutic and diagnostic approaches which are used to better overcome the viral disease covered widely in this review. Despite controversial opinions about the virus origins and the main purposes, only once the pandemic infection ends, we shall be able to assess and shed the light on the impact of this worldwide disaster. Moreover, we shall improve our public, global, diagnostic, and therapeutic tools in which this will be helpful for any future pandemic that shall arise later on perhaps due to a natural origin or diplomatic and economic purposes. Without fundamental therapeutic interventions, current management is to reduce the virus spread and provide supportive care for diseased patients. There is an urgent need to develop targeted therapies. Understanding the disease and the different responses to this virus could help to find immune-based therapeutics or/and traditional medicines.

Ethical Considerations

The identities of patients remained unknown and their identities remained confidential and only used for research purposes. The procedures were accomplished upon obtaining permission from the Ethical Committee of Hebron University.

Conflict of Interest and Financial Disclosure

The authors declare no competing financial interests and no conflicts of interest with respect to the authorship and/or publication of this article.

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