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REVIEW ARTICLE

SARS-CoV-2: a review for clinicals

SARS-CoV-2: uma revisão para clínicas

SARS-CoV-2: una revisión para clínicos

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ABSTRACT

Background and Objective: The COVID-19 pandemic raises greater knowledge about the disease. The objective is to elucidate this new disease that affects all continents of the planet. **Design And Setting:** A narrative review of clinical aspects of COVID-19. **Methods:** A review was carried out with the studies with the greatest clinical evidence from the Pubmed database by researching the descriptors "COVID-19", "coronavirus" OR "SARS-CoV-2" AND "[topic]". **Results And Discussion:** Epidemiology: The infection reached the mark of 11,000,000 patients, 530,000 deaths and raised the presence of comorbidities and advanced age as risk factors. Transmissibility: The calculated transmissibility is similar to the H1N1 epidemic, however with a lower mortality rate. Physiopathology: The SARS-CoV-2 virus, a beta-coronavirus, is capable of cell invasion through the fusion of glycoprotein S with the angiotensin-converting enzyme 2 present in the lower respiratory epithelium and cells of the lower respiratory epithelium mucosa of the digestive tract. Clinical Manifestations: the presentation can be divided into mild (fever, fatigue, cough, myalgia and sputum) and severe (cyanosis, dyspnoea, tachypnea, chest pain, hypoxemia, respiratory failure) and has an estimated mortality of just over 4%. It can generate thrombotic events and neurological and autoimmune syndromes. Diagnosis: It occurs through the detection of viral load in the reverse transcription polymerase chain reaction (CRP-TR). Treatment: Based on supportive and infection control measures. In severe cases, the use of medications such as remdesevir 200 mg intravenously in a single dose on day 1, followed by 100 mg in single daily doses from D2 to D5 and dexamethasone 6 mg orally in every 24 hours can be promising. **Conclusion:** The COVID-19 pandemic is a potentially serious disease and still has no specific treatment.

Key Words: *Coronavirus. COVID-19 [Supplementary concept]. Severe acute respiratory syndrome coronavirus 2 [Supplementary concept]. Pandemics. Review [Publication type].*

RESUMO

Justificativa e Objetivo: A pandemia de COVID-19 traz maior conhecimento sobre a doença. O Objetivo é elucidar esta nova doença que atinge todos os continentes do planeta. **Tipo de estudo e Local:** Uma revisão narrativa dos aspectos clínicos da COVID-19. **Métodos:** Foi realizada uma revisão dos estudos com maior evidência clínica da base de dados Pubmed pesquisando os descritores "COVID-19", "coronavirus" OR "SARS-CoV-2" AND "[tópico]". **Resultados e Discussão:** Epidemiologia: A infecção atingiu a marca de 11 milhões de pacientes, 530.000 óbitos e elevou a presença de comorbidades e idade avançada como fatores de risco. Transmissibilidade: A transmissibilidade calculada é semelhante à epidemia de H1N1, porém com menor taxa de mortalidade. Fisiopatologia: O vírus SARS-CoV-2, um beta-coronavírus, é capaz de invasão celular por meio da fusão da glicoproteína S com a enzima conversora de angiotensina 2 presente no epitélio respiratório inferior e células da mucosa do epitélio respiratório inferior do aparelho digestivo trato. Manifestações clínicas: a apresentação pode ser dividida em leve (febre, fadiga, tosse, mialgia e expectoração)

e grave (cianose, dispneia, taquipneia, dor torácica, hipoxemia, insuficiência respiratória) e tem mortalidade estimada em pouco mais de 4%. Pode gerar eventos trombóticos e síndromes neurológicas e autoimunes. Diagnóstico: ocorre pela detecção da carga viral na reação em cadeia da polimerase de transcrição reversa (CRP-TR). Tratamento: Baseado em medidas de suporte e controle de infecção. Em casos graves, o uso de medicamentos como remdesevir 200 mg por via intravenosa em dose única no dia 1, seguido de 100 mg em dose única diária de D2 a D5 e dexametasona 6 mg por via oral a cada 24 horas pode ser promissor. **Conclusão:** A pandemia de COVID-19 é uma doença potencialmente grave e ainda não possui tratamento específico.

Palavras-Chave: *Coronavírus. COVID-19 [conceito complementar]. Síndrome respiratória aguda grave coronavírus 2 [conceito suplementar]. Pandemics. Revisão [tipo de publicação].*

RESUMEN

Antecedentes y Objetivos: La pandemia de COVID-19 aumenta el conocimiento sobre la enfermedad. Dilucidar esta nueva enfermedad que afecta a todos los continentes del planeta. DISEÑO Y AJUSTE: Una revisión narrativa de los aspectos clínicos de COVID-19. **Métodos:** Se realizó una revisión de los estudios con mayor evidencia clínica de la base de datos Pubmed investigando los descriptores "COVID-19", "coronavirus" O "SARS-CoV-2" Y "[tema]". RESULTADOS Y **Discusión:** Epidemiología: La infección alcanzó la marca de 11.000.000 de pacientes, 530.000 muertes y planteó la presencia de comorbilidades y edad avanzada como factores de riesgo. Transmisibilidad: La transmisibilidad calculada es similar a la epidemia de H1N1, pero con una tasa de mortalidad más baja. Fisiopatología: El virus SARS-CoV-2, un beta-coronavirus, es capaz de invasión celular mediante la fusión de la glicoproteína S con la enzima convertidora de angiotensina 2 presente en el epitelio respiratorio inferior y las células de la mucosa del epitelio respiratorio inferior del aparato digestivo. tracto. Manifestaciones clínicas: la presentación se puede dividir en leve (fiebre, fatiga, tos, mialgias y esputo) y severa (cianosis, disnea, taquipnea, dolor torácico, hipoxemia, insuficiencia respiratoria) y tiene una mortalidad estimada de poco más del 4%. Puede generar eventos trombóticos y síndromes neurológicos y autoinmunes. Diagnóstico: Se produce mediante la detección de carga viral en la reacción en cadena de la polimerasa con transcripción inversa (CRP-TR). Tratamiento: Basado en medidas de apoyo y control de infecciones. En casos graves, el uso de medicamentos como remdesevir 200 mg por vía intravenosa en una sola dosis el día 1, seguido de 100 mg en dosis únicas diarias de D2 a D5 y dexametasona 6 mg por vía oral cada 24 horas puede ser prometedor. **Conclusión:** La pandemia de COVID-19 es una enfermedad potencialmente grave y aún no tiene un tratamiento específico.

Palabras Clave: *Coronavirus. COVID-19 [Concepto complementario]. Síndrome respiratorio agudo severo coronavirus 2 [concepto complementario]. Pandemias. Revise [Tipo de publicación].*

INTRODUCTION

On December 31, 2019, several cases of pneumonia linked to a seafood market in Wuhan, China, were reported to the World Health Organization (WHO). The infection displayed a quick spread rate, and is now known as 2019 coronavirus disease (COVID-19) that is caused by a new coronavirus (SARS-CoV-2). Given the escalation of this infectious disease, it is mandatory to deeply examine the aspects of the natural history of this disease. Its diagnosis and treatment are essential to elucidate this new disease that affects all continents of the planet.

OBJECTIVE

To elucidate this new disease that affects all continents of the planet.

METHODS

This is a narrative review in which articles were selected from the PubMed database by researching the descriptors "COVID-19", "coronavirus" OR "SARS-CoV-2" AND "[topic]". The topic was chosen considering the main aspects of the natural history of the disease, namely: epidemiology, transmissibility, etiology, pathophysiology, clinical manifestations, diagnosis and treatment. Priority was given to papers with the highest level of Oxford evidence (systematic reviews and randomized controlled trials), when these were made available. In vitro and relevant animal model research were included in this study. Other works outside these databases were included due to their relevance to the topic. This review took place between January 28, 2020 and July 5, 2020 and the summary of methods are below. As the study is based on a review of public data and without explicit reference to patients/participants, approval by the Research Ethics Committee was not required (according to CNS resolution nº 466/120).

RESULTS AND DISCUSSION

In our search, 1,272 articles were found. After removing duplicates (20), comments (57), editorials (78), correspondence (65) and articles without correlation with the topic (967), we obtained 85 articles. The topics are showed below.

Epidemiology

The World Health Organization declared a pandemic 71 days after the discovery of the new coronavirus.[1] Currently, more than 11 million cases and 530 thousand deaths have been confirmed, with a global lethality rate of 4.7%.[2] An important global economic impact is estimated with a wide recession following saturation of health services, as well as the halt of non-essential activities during the period of greater transmissibility.[3] The average age of the infected varies between 49 and 56 years, and symptomatic individuals under 20 years of age are rare.[4] The severity of the condition is correlated with advanced age (mean age of death in Italy is 79.5 years), severe obesity, and with cardiovascular as well as pulmonary comorbidities.[4-7]

Transmissibility

The transmission of SARS-CoV-2 occurs mainly by airborne particles and fomites.[4,8] In airborne particles, viruses remained stable for 7 hours, both in aerosols (particles smaller than 5 micrometers) and in droplets (particles larger than 5 micrometers), presenting half-life of 2.7 hours.[9] Fomites are crucial for the transmission of SARS-CoV-2, since it can persist for up to 9 days on smooth surfaces such as metals and plastics and up to 48 hours on porous surfaces, being sensitive to disinfection by 62-71% ethanol, 0.5% hydrogen peroxide or 1% sodium hypochlorite in up to 1 minute of exposure. Other materials were not effective (chlorhexidine and benzalkonium).[10] Oral-fecal and intrauterine vertical transmission were also described but are less frequent.[11-13]

The quantification of transmissibility is given by R_0, with R_0 less than 1 indicating that each infected patient generates less than one new infection, R_0 equal to 1 indicating that the disease will remain but will not generate an epidemic, and R_0 greater than 1 meaning that it generates an epidemic with exponential growth of new cases. R_0 transmissibility is calculated from four variables, namely: duration of the transmission period (includes three days before the onset of symptoms until the end of the symptomatic period), opportunity (how many individuals had contact with the infected person), probability of transmission and susceptibility (at the beginning of the pandemic, it was around 100%). It is also important to note that R (effective reproduction number) is different from R_0 (basic reproduction number), given that the former is calculated as a variable from the public health measures implemented and the latter is calculated as intrinsic to the agent and population studied. Thus, the R_0 of SARS-CoV-2 scores between 1.4 and 5.5, being calculated a priori as 2.6. That is, each infected person has the capacity to generate 2.6 new infections. Comparatively, this rate is higher than other respiratory infections by coronaviruses (SARS-CoV 2-5, MERS-CoV < 1) and by other respiratory agents (H1N1 1918 1.4-3.8, H1N1 2009 1.2-1.6), but lower than other pandemics (Measles 12-18, Smallpox 5-7).[8,11-13] Transmissibility seems to be reduced in hot and humid climates and may change seasonally.[14-16]

Etiology

Coronaviruses are a family of positive-sense simple ribonucleic acid (RNA) genome viruses (ribbon directly serves for protein synthesis), first discovered in animals in the 1930s. The main human pathogens belong to the taxonomic subfamily Orthocoronavirinae and the order Nidovirales.[17,18] Only seven entities of this family display pathogenicity to the human species, four of which are implicated in common cold symptoms (alpha-coronavirus 229E and NL63 and beta-coronavirus OC43 and HUK1) and three with the ability to cause more severe respiratory infection in humans (SARS-CoV, MERS-CoV and SARS-CoV-2).[8,19] SARS-CoV-2 is the new betacoronavirus identified on 31/12/2019 as the etiological agent of disease by the 2019 coronavirus (formerly known as COVID-19). It was first described in Wuhan, China, and belongs to the subgenus sarbecovirus. SARS-CoV-2 is believed to originate from chiropterous mammals (bats), as they have been reported to a local animal trade in Wuhan, as well as their close genetic resemblance to infective coronaviruses of this genus.[8, 20,21]

Physiopathology

Conducting a brief summary of respiratory histology and physiology, it is known that the pulmonary epithelium has two main types of angiotensin-converting enzyme (hereinafter referred to as angiotensin conversion enzyme (ACE)), being ACE related to the conversion of angiotensin I into angiotensin II, culminating in vasoconstriction and cardiac remodelling. However, ACE2 is a membrane-bound carboxypeptidase with the function of cleaving a single residue of angiotensin I (generating Ang 1-9) and a single residue of angiotensin II (generating Ang 1-7), whose functional vasodilator, antiproliferative and antifibrotic effects are opposed to those of Ang II generated by the angiotensin conversion enzyme (ACE). It is known that by inhibiting ACE (with angiotensin-converting--enzyme inhibitors (ACEI) and ARB antihypertensives) the number of ACE2 in the renal epithelium membrane and in the heart is increased, with theoretical potential to increase in other tissues as well. It is also known that the ACE and ACE2 enzymes are present in other tissues besides the lung (alveolar epithelial cells type I and II) and the heart, as in the entire digestive tract (in high density in the oral cavity) and also in the renal epithelium.[22,23]

Studies indicate that SARS-CoV-2 exploits the same angiotensin converting enzyme 2 (ACE2) as SARS-CoV to gain access to target cells, although it has a higher binding affinity. After contagion, the entry of SARS-CoV-2 begins with the binding of the glycoprotein S expressed in the viral envelope to ACE2 on the alveolar surface. The binding of SARS-CoV-2 to ACE2 stimulates clathrin-dependent endocytosis of the entire SARS-CoV-2 and ACE2 complex, inducing fusion in the cell membrane. Entry of SARS-CoV-2 endosomal cells is facilitated by endosomal catepsins (low pH and pH-dependent endosomal cysteine proteases, hence the chloroquine use theory, due to its potential to raise the endosomal pH in vitro and to prevent the entry of the etiologic agent into the cell).[22] However, the use of chloroquine has not been shown to alter patient mortality and its use will be discussed on the appropriate topic.[24]

Once inside the cells, SARS-CoV-2 explores the endogenous transcriptional mechanism of alveolar cells to replicate and spread throughout the lung tissue. When SARS-CoV-2 infects most alveolar hair cells, these cells interrupt their normal activity, with a consequent progressive accumulation of debris and fluids in the lungs and progression to acute respiratory distress syndrome (ARDS).[22] There is the possibility of bacterial superinfection, given the aforementioned pathophysiology and the biphasic clinical picture (evolution to ARDS after 5-8 days of illness). This second part of the pathophysiology would corroborate the use of azithromycin, in addition to its supposed effects on viral reproduction. However, azithromycin alone has not shown significant results.[24]

Despite the potential for the aforementioned ACE inhibitors to potentiate a severe clinical picture, in vitro studies suggest that increased ACE2 attenuates lung injury caused by SARS-CoV-2 infection. The use of ACEIs and ARBs may be protective due to the increased expression of ACE2, which could induce the sequestration of SARS-CoV-2 in the cell membrane without being able to effectively enter the intracellular environment in order to reduce the viral load, therefore acting as a "decoy receptor" (if this theory is true, camostat mesilate may prove to be a valuable option for combating this virus). Moreover, it is likely that the increase in angiotensin II available from the ARBs will generate competition with SARS-CoV-2 by ACE2, with greater cleavage in angiotensin 1-7 (as mentioned above) and promoting a cytoprotective environment in the lungs (despite the vasoconstriction and prophyrotic processes generated by SARS-CoV-2 and angiotensin II).[22,23,25]

Studies indicate that the viral load detected in asymptomatic patients was similar to that found in symptomatic patients (these, however, present clearance in less time than those); however, the viral loads of patients with severe diseases were higher than those of patients with mild to moderate presentations. Moreover, higher viral loads were detected in the nasal mucosa than in the oropharynx, suggesting greater efficacy of the upper swab in the nasal mucosa, in addition to lower risk to the professionals involved in collection.[26]

The incubation period varies from 2 to 14 days (average of 5.2 days). The average time between the first symptoms and the development of acute respiratory distress syndrome (ARDS) is eight days.[27] A possible explanation for this quick and severe deterioration is the cytokine release syndrome, or "cytokine storm", an overproduction of immune cells and cytokines that leads to rapid multiple organ failure and fatal damage to lung, kidney and heart tissues. Studies indicate that this cytokine storm may be related to the development of autoimmunity and type 1 diabetes.[28] The presence of a hypercoagulant state was also reported, with microthrombi and severe endothelial lung and intestinal injury,

coinciding with the course of SARS-CoV-2 infection.[29,30]

The current tendency to release convalescent individuals from quarantine COVID-19 raises the hypothesis of whether or not there could be reinfection. Although other coronaviruses make reinfection possible and there are cases reported in COVID-19 of this process, there is no elucidation so far as to whether this possibility exists. It is known that infection with other coronaviruses triggers a short and medium term cross-response that leads to new early re-infections in humans. A research carried out in primates was not able to demonstrate the presence of COVID-19 re-infection.[31] Limited current data reinforce the idea that short- and medium-term re-infection is not possible.[32] In addition, there is a hypothesis that patients previously infected with SARS-CoV-2 who tested positive again in PCR-TR tests present only false-positive with inoperative virus (and not a re-infection), given their limited growth capacity in culture.[33] Long-term serological studies are needed to determine whether and for how long neutralizing antibody levels are sustainable.

Clinical manifestations

Cohorts indicate that up to 88% of patients are totally asymptomatic or display only mild and non-specific symptoms.[34,35] Mild to moderate cases may initially present with anosmia and ageusia (pre-hospitalization symptom in up to 91% of patients),[36,37] later evolving to fever, fatigue, cough, myalgia, sputum, nausea, headache, amenesis, abdominal pain, diarrhea, odinophagia, and rhinorrhea.[14] Fever, cough, fatigue, and dyspnea were the most frequent symptoms, including pediatric patients, although almost 20% of these were asymptomatic.[38-40]

The initial findings of anosmia and ageusia tend to recede in most patients within four weeks of the onset of symptoms.[37]

Severe cases (10-15%) may present chest pain, cyanosis, dyspnea, tachypnea, signs of respiratory effort, hypotension, decompensation of underlying diseases, and lymphopenia should be conducted in a hospital bed.[41,42] Respiratory rate (RR) > 30 irpm, oxygen saturation (SatO2) < 93%, arterial oxygen partial pressure/ fractional inspired oxygen (PaO2/ FiO2) < 300 were factors of poor prognosis and evolution to mechanical ventilation (risk factors for mechanical ventilation: hypertension, diabetes mellitus and age over 65 years). A study with 1,000 patients identified that of patients requiring intensive care, 78% had acute kidney injury at some point, requiring hemodialysis in 35.2%.[43] In those patients requiring intensive care, mortality reached 26%.[42]

Other reported manifestations include early gastrointestinal manifestations (diarrhea and fever) in immunosuppressed patients and skin manifestations on the trunk (including erythematous rash and generalized urticaria) and varicella-type vesicles (one patient).[44,45] Thrombotic and neurological manifestations, including strokes, were reported during the clinical course of the disease.[29,30,46,47,48] A study with almost 2,000 patients, comparing incidence of ischemic strokes in patients with COVID-19 and influenza found an incidence 8 times higher, with odds ratio, 7.6 and 95% confidence interval (CI), 2.3-25.2.[47] Association with Kawasaki's disease in children and Guillain-Barré syndrome and Miller-Fisher syndrome were also described.[49-51] Due to pathological accumulation of amyloids in the nervous tissue of guinea pigs, the hypothesis of an association between Alzheimer's disease and infection with the new coronavirus was suggested.[52]

Laboratory studies have shown that the main changes described were namely a reduction in albumin (75%), an increase in C-reactive protein (58%) and in lactate dehydrogenase (57%).[53] Lymphopenia (despite leukometry within normal limits) and changes in liver and canalicular enzymes (gamma-glutamyl transferase (GGT), aspartate aminotransferase (AST) and bilirubin) in up to 54% of patients and it was possible to isolate SARS-CoV-2 in cerebral spinal fluid (CSF).[12,46] The most common finding in chest computed tomography (CT) scans in patients was nodular opacity in frosted glass with peripheral and bilateral involvement of lower lobes in 68.5%. Such findings may occur even in asymptomatic patients, but are more common in patients with COVID-19-related pneumonia. The presence of thin fibrotic layer (fine reticular opacities) indicates good prognosis of the disease, with evolution in remission.[26, 53, 54]

Convalescence lasts from one to three weeks for mild cases and from two to six weeks for severe cases.[55] In this period, it is still possible to have positive PCR-TR in most patients, however the clinical significance is uncertain and there is no evidence of the possibility of infection.

Diagnosis

Clinical suspicion follows the presence of new fever and respiratory tract symptoms (cough, dyspnea). The presence of a compatible epidemiology (contact with a suspected or confirmed case, travel to an endemic site for less than 14 days, residence at a community-transmitted site) increases the suspicion of SARS-CoV-2 over other respiratory syndromes and should indicate a PCR-TR test.[26] Diagnosis is currently only possible by PCR-TR positive.[56] It is important to remember that the PCR-TR test is more sensitive when performed from day three of symptoms and the rapid serological test is more sensitive from day eight of onset of symptoms. Thus, once there is suspicion and the test is negative, a new test is then directed from seven days or from the above-mentioned dates.[56] There is insufficient evidence to indicate the large-scale use of commercial serological tests, since studies indicate low sensitivity (49.0% to 78.2%), and a false negative may generate risk behaviour in the population. The non-commercial immunoassays quioluminescent showed satisfactory sensitivity and specificity (98% in both questions), respecting the minimum time of 7 days from the onset of symptoms to perform the test.[57]

Treatment and public health measures

Currently, the only treatment endorsed by the World Health Organization is clinical support.[20,21,27,58] The treatment of mild to moderate cases is based on antipyretics and hydration.

Epidemiological measures for infection control management should be performed.

Mild cases should be treated as outpatients, requiring domestic isolation with contactant orientation regarding hygiene (patient restricted to the closed and well-ventilated door room, vomiting should be sanitized with water and soap or 70° alcohol by the infected person himself, minimal agitation and handling of clothing, frequent hygiene of contactant and patient hands, quarantine of domestic contactants for 15 days).[56,58] These patients should ideally be accompanied by the primary care team each 48 hours via telephone or teleconsult. It is recommended to guide return if it worsens clinically and to offer domestic contactors leave of absence from work for 14 days. It is recommended to emphasize the need for care in domestic environments, since it is remarkable the high transmissibility in it, especially in low-income families and with more than four individuals at home.[27,56,59]

Severe cases (SatO2 < 95%, tachypnea, tachycardia, decompensation of comorbidities) should be hospitalized in isolation in a room with negative pressure, individually or two meters away from other suspected cases and precautions should be taken. Hand washing and correct use of personal protective equipment (PPE) by healthcare professionals is indicated (gloves, disposable cloaks, N95 mask in case of entering

a room or invasive procedure, cap and face protection). It is important to observe the need of providing masks to symptomatic respiratory patients already at the hospital reception and to provide a separate waiting room, as well as to limit the number of companions.[27,56]

General measures such as oxygen supplementation if SatO2 lower than 94%, hydration, symptoms and control of decompensated comorbidity are recommended. When prescribing discharge, guide the patient about the biphasic clinic and possible worsening after 5-8 days from the onset of symptoms.[27,56] For patients in a preoperative routine, it is recommended to postpone the procedure (if possible), since there is a higher postoperative morbidity and mortality.[60]

In case of systolic blood pressure (SBP) < 90 mmHg, diastolic blood pressure (DBP) < 60 mmHg or persistence of SatO2<94% despite supplementation with nasal catheter 5 l/minute, a follow-up in intensive care unit (ICU) bed and early OTI is indicated. Non-invasive ventilation (NIV) should be used with caution: although it is effective in preventing intubation in patients with respiratory discomfort, it can generate droplet dispersion in the sector and is indicated for 30 minutes only if the private room has negative pressure. Prone position in these patients, including the conscious hypoxemic ones, was related to the improvement of oxygen saturation levels and reduction of the evolution to orotracheal intubation, being recommended if the patient is accepted.[61] Thus, negative hydric balance of 0.5-1 L/day is recommended in case of ARDS, maintenance of mean arterial pressure (MAP) between 65-70 mmHg (in cases of shock, provide isotonic hydration 30 ml/kg, proceeding later to vasoactive drugs if refractory), protective mechanical ventilation (tidal volume 4-8 mL/kg, plateau pressure < 30 centimeters H2O, positive end-expiratory pressure (PEEP) following ARDSNet table), intermittent night sedation for early weaning, prevention of deep vein thrombosis (DVT) (stimulate walking). Use of intermittent compressive stocking/pneumatic compression, low molecular weight heparin), correction of acid-base and hydroelectrolytic disorders, prevention of nosocomial infection (ventilator related pneumonia, catheter related infections), prevention of decubitus ulcer (2/2 hours decubitus change) are essential and should be implemented in cases of COVID-19.[56,58]

Regarding specific drug treatment, a proven effective drug is still awaited. The main drugs under study are hydroxychloroquine associated or not with azithromycin, remdesevir, dexamethasone and heparin. In in vitro studies and initial non-randomised, small sample trials, hydroxychloroquine (antimalarial) and azithromycin (macrolide antibiotic) proved promising.[62-66] However, more controlled studies of more reliable methodology using hydroxychloroquine and azithromycin alone or in combination failed to show statistical difference for mortality parameters and days of hospitalization, as well as benefit in the prophylactic use of chloroquine.[67-71] There is little recommendation for use of these drugs.

The use of remdesevir, an antiviral RNA inhibitor polymerase initially developed for the treatment of ebola,[72] proved promising. Final reports of controlled clinical trials and systematic reviews are awaited, however preliminary data indicate a significant reduction in hospitalization time and viral load, as well as a controversial reduction in mortality, both in treatment groups for 5 days and in treatment for 10 days.[73-78] The dosage studied was of 200 mg intravenously in a single dose on day 1, followed by 100 mg in single daily doses from D2 to D5. It was noted that the early onset of the antiviral (less than 10 days from the onset of symptoms) correlated with reduced mortality and hospitalization.[76,77] The recommendation of use is moderate, with restricted use to severe patients and under hospitalization regime. Use in patients with liver disease and with a glomerular filtration rate below 30 mL/minute/1.73 is not recommended.

Regarding dexamethasone, its use was previously condemned due to previous experiences with MERS (which generated a delay in viral clearance) and due to initial negative experiences with SARS-CoV-2 (which promoted a worse clinical outcome, decompensation of diabetes mellitus psychosis, being previously recommended only in case of septic shock or documented adrenal insufficiency).[26,44] However, in recent trials, including the RECOVERY study – not yet published and submitted to peer review – dexamethasone 6 milligram/day was shown to be beneficial for participants treated 7 or more days in the symptomatic phase, obtaining a mortality rate 8-26% lower than 4,321 participants who received standard treatment.[79-81] It is important to note that there was a non-significant tendency for possible damage to participants without hypoxemia and who were not on mechanical ventilation. Therefore, RECOVERY's findings support the use of dexamethasone only in symptomatic patients with hypoxemia, not in those with mild disease. The data do not support the use of dexamethasone or other corticosteroids in the ambulatory.[79] Due to recent studies, some of which are not yet published, there is no degree of usage recommendation, however when prescribed, the authors indicate hospital use in symptomatic hypoxemic patients.

Due to recent findings of severe endothelial injury and hypercoagulant state,[29,30] the hypothesis of anticoagulation in a therapeutic dose of low molecular weight heparin has been suggested. Initial observational and experimental studies with questionable methodology presented promising results, with improved prognosis and reduced mortality of patients admitted under intensive care.[82-84] Careful use of anticoagulants is recommended only in patients with proven septic shock, given the statistically significant risk of bleeding, as well as the absence of studies with adequate methodology on the subject.

Although other drugs under study show reduced mortality and length of stay in intensive care, they do not present a recommendation or present a recommendation contrary to the use by National Institutes of Health (NIH) (mainly due to lack of strong evidence and potential risk of serious adverse effects or unfavorable pharmacokinetics). This topic includes drugs such as colchicine, lopinavir + ritonavir + ribavirin, interleukin 6, nebulization with interferon and immunoglobulins.[85,86]

A recent review including 11,321 people in 14 countries demonstrated that vitamin D supplementation decreased the risk of acute respiratory infections (ARIs) in both those with vitamin D deficiency and those with adequate levels.[87] Studies with a low level of evidence have justified the prophylactic and therapeutic use of vitamin D;[88,90] however specific and more reliable studies for SARS-CoV-2 are needed to elucidate the real application of these results during this pandemic.

It should be noted that discontinuing ACEs and ARBs antihypertensives is not recommended due to potential for cardiac decompensation, as well as not using ibuprofen – when there is no other alternative to this nonsteroidal anti-inflammatory drugs (NSAID) – is inadvisable.[26,44,91,92] Passive immunoprophylaxis with convalescent serum in mice showed a significant reduction in viremia, however it did not significantly alter the evolution to pulmonary disease.[84]

Measures such as auto-quarentine or temperature control at borders should not be very effective, since most infections are asymptomatic/pre-symptomatic and 44% of the patients on examination are affective. The most effective measure today is mass testing with home isolation of positive (even asymptomatic) cases. Such measurement is necessary since there is evidence that asymptomatic and pre-symptomatic patients successfully transmit the infection to new infectees.[93-96]

Cruise ships, due to the controlled environment, provide a sine qua non study of transmissibility, being able to differentiate true asymptomatic, paucisymptomatic, and presymptomatic patients and to trace the index infection. In these studies, the wide dissemination despite the isolation of the positive ones raises the hypothesis of transmission by asymptomatics, although other studies indicate that this generation of new cases from asymptomatics occurs only in 0.3% of the counted cases, compared with 5% from symptomatic cases.[96]

Furthermore, there is currently a consensus to propose the closure of schools (children in general are asymptomatic, although they have the potential to be over-disseminating and can generate up to 80 new infections), to restrict social gatherings (including restricting events with large numbers of people and closing workplaces), to limit population movements and to introduce so-called health cordons (quarantines on the scale of cities or regions). This institution of interventions (including cordons sanitaire, traffic restriction, social distancing, centralized quarantine, and universal symptom research) was temporally associated with reducing the effective number of reproduction of SARS-CoV-2 (secondary transmission) and the number of confirmed cases per day in age groups, sex, and geographic regions.[27,97]

In intra-hospital settings, social distancing among employees, restricting the number of contacts without individual protection equipments (IPEs) (such as breaks and lunches); respiratory and hand hygiene; mass testing of professionals with isolation of positives and restriction of intra-institutional and extra-institutional mobility of health professionals, especially for those directly involved with respiratory symptomatic patients are all recommended measures.[27,97] The provision of IPEs and the awareness of employees is essential. Knowing the scarcity of masks, it was proposed to study the filtration efficiency of surgical masks and N95 after sterilization with some materials, both of which maintained good results after a sterilization cycle with hydrogen peroxide. There is a need for other confirmatory studies as well as analyses of filtration efficiency after multiple cycles; however, this opens the possibility of mask reuse after treatment with hydrogen peroxide.[98]

The use of fabric masks has been recently recommended due to this same shortage of PPE, but presents a lack of evidence of protection. A randomized controlled clinical trial identified a statistically significant increase in risk (relative risk 13.00, 95% CI 1.69 to 100.07) of infection from wearing tissue masks compared to disposable surgical masks, warning that moisture retention, reuse of cloth masks and insufficient filtering may result in an increased risk of infection.[99]

A return to normal daily activities remains uncertain. It is suggested that with universal testing, non-transmitter convalescents (immunoglobulin G (IgG) positive PCR-TR negative) may return from isolation and collaborate with the production chain (reduction of lockdown). Recently, the World Health Organization suggested the possibility of loosening quarantine for regions with controlled rates of transmissibility, a health system capable of detecting, isolating and treating all new infectees, control of the risk of importing cases, and sanitary control of places at risk (such as institutions in which prolonged stays takes place), as well as a social community that is aware and able to comply with the new standard.[27,100]

CONCLUSION

The COVID-19 it is a potentially serious disease and still has no specific treatment. Randomized clinical trials and more genetic research are expected to elucidate still obscure points of the disease.

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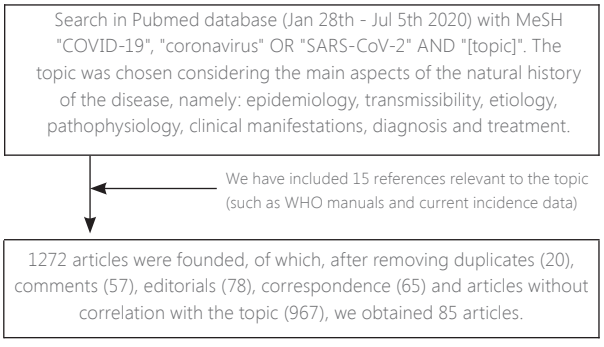

Figure 1. Summary of research and results of articles found.