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Review Article

COVID-19: Aspects of outpatient treatment

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Abstract

Background: Coronavirus Disease 2019 (COVID-19) has become a significant public health crisis and one of leading causes of death internationally. Although, most infected people develop smooth symptoms and are treated ambulatory, only few studies focus on outpatient care. Thus, there is crucial need of recommendations for therapeutic strategies in outpatient care. Aim of this study was to focus on relevant aspects regarding outpatient care in General Practice.

Methods: An open search for pertinent publications was conducted through PUBMED search using keywords like "medical treatment", "therapeutic strategies", "COVID-19", "SARS-CoV-2", **"**ambulatory", **"**outpatient", and with their corresponding MeSH terms, if any, connected by OR and AND. Snowball technique was used to gather further relevant papers from the reference lists of the initial search result articles. Most important results regarding COVID-19 ambulatory care are presented for daily use in General Practice.

Results: Antiviral drugs cannot yet be generally recommended for regular use in outpatient care as no significant benefit was seen so far. For immunomodulatory drugs convincing data is missing supporting its efficacy and safety for COVID-19 management. Dexamethasone, budesonide turbohaler, methylprednisolone and prednisone should be regarded for outpatient treatment. Use of low-molecular weight heparin is beneficial to reduce risk of thrombosis. Several adjuvant therapeutics as tramadol, statins, thiamine, and ascorbic acid can be considered as supportive. Different natural products show promising effects, but much more investigation is necessary to give final advise. Preventive effects of zinc and vitamin D are still under discussion, no strong recommendation can be given so far. Most important, supportive care including supplemental oxygen, monitoring, and telemedicine should be available.

Conclusion: Recommendations for daily ambulatory routine include a multi-pronged therapeutic approach in COVID-19 outpatient care. Most important strategies in therapy involve symptomatic supportive treatment along with anti-inflammatory therapies including corticosteroids. Prohibition of severe COVID-19 cases requires early identification and acceleration of vaccination process.

Keywords: SARS-CoV-2, COVID-19, Outpatient, Ambulatory, Treatment, Immunomodulation

Clinical Relevance

Most important aspects of COVID-19 outpatient care are discussed: general strategies, immunomodulation, antithrombotic therapy, adjuvant therapy, and prevention. Reduction of COVID-19 hospitalizations and death can be achieved by improved outpatient treatment.

Background

Coronavirus Disease 2019 (COVID-19) currently has become a significant public health crisis and one of leading causes of death internationally [1]. A considerable number of cases progresses to pneumonia with severe respiratory failure. So far, many studies address reduction of inpatient mortality and containment of the spread of infection. Nevertheless, most infected people develop smooth symptoms and are treated ambulatory [2,3]. Thus, there is crucial need of recommendations for therapeutic strategies in outpatient care. To date, no specific therapy against COVID-19 disease exists [4]. Novel therapies will be needed to reduce the morbidity and mortality associated with the

virus [1]. This article focuses on therapeutic strategies in ambulatory treatment of COVID-19-patients.

Methods

An open search for pertinent publications was conducted through PUBMED search using keywords like "medical treatment", "therapeutic strategies", "COVID-19", "SARS-CoV-2", "coronavirus", "2019-nCoV", "ambulatory", "outpatient" and with their corresponding MeSH terms, if any, connected by OR and AND. No search filters were applied, and snowball technique was used to gather further relevant papers from the reference lists of the initial search result articles.

Combined Results and Discussion

Pathophysiology

In COVID-19, dysregulated inflammation and coagulation is observed, similar to that of multifactorial ARDS [5,6]. Lung epithelial cells are the primary target of SARS-CoV-2, and the first step of viral infection involves its binding to angiotensin converting enzyme (ACE-2) receptors expressed on the host cells followed by fusion with the cell membrane [7]. Several chemokines and cytokines are involved in infection, which include tumor necrosis factor (TNF)-α, interleukin (IL)-6, IL-7, IL-8, IL-9, IL-10, IL-1, granulocyte colony stimulating factor (G-CSF), and interferon (IFN)-γ amongst others [7]. Believed to be linked directly to the 'cytokine storm' are the two most dreaded complications of COVID-19: acute respiratory distress syndrome (ARDS) and multi-organ failure [8]. Further, COVID-19 may lead to hypercoagulable condition as patients present with prominent elevation of D-dimer and fibrin/fibrinogen degradation products comparable to traditional disseminated intravascular coagulation DIC [9]. Tests show either little or no abnormalities in prothrombin time (PT), partial thromboplastin time (PTT), and platelet counts initially [10].

Antiviral therapy

It has proven challenging to find antivirals that reduce mortality from severe respiratory viral infections as COVID-19 [11]. The characteristic immunopathology of COVID-19 shows an initial phase of intense viral replication that progresses to respiratory failure at day 8–9 in severe infections due to the host inflammatory response [12]. Thus, there might be an opportunity for the use of antivirals before fulminant inflammation sets in and reaches the peak of viral replication [13]. A trend towards reduced mortality using remdesivir could be found among patients requiring low-flow or high-flow oxygen at baseline [14]. But, for ambulant patients with mild or moderately severe COVID-19, remdesivir does not offer significant benefit and is not recommended if patients have no need for respiratory support [15]. Regarding use of broad-spectrum antiviral drugs like neuraminidase inhibitors, ribonucleic acid (RNA) synthesis inhibitors, nucleoside analogues, and human immunodeficiency virus (HIV)-protease inhibitors current evidence base supporting their use is rather weak [16]. Several other antiviral drugs, such as Lopinavir–ritonavir [17], have been previously investigated and discussed but up to date there is no evidence for indication in ambulant therapy [4]. Another potential candidate is favipiravir (oral drug). It was approved for pandemic influenza in Japan in 2014 and has shown effects in clinical studies in China, Russia, and Japan for COVID-19 [18]. Significant clinical and radiological improvement was seen for favipravir in comparison to the standard of care but there was no significant difference on viral clearance, oxygen support requirement and side effect profiles [19,20]. Although favipiravir has strong possibility for treating COVID-19, especially in patients with mild-to-moderate illness, well-designed studies, including examinations of the dose and duration of treatment, are crucial for final evaluation [21]. It can be concluded that remdesivir and other antiviral drugs are not yet recommended for patients with mild or moderately severe COVID-19 and no need for respiratory support [15].

Immunomodulatory drugs

Chloroquine (CQ) and hydroxychloroquine (HCQ) are antimalarial drugs and have an extremely broad spectrum of action being effective against viruses, bacteria, fungi, and protozoa [4]. HCQ received significant media and political attention [22] as prophylaxis of COVID-19. But there is lack of convincing and unequivocal data supporting its efficacy and safety for COVID-19 management [23,24] and thus should not be used regularly in outpatient care. Efficacy of CQ or HCQ in preventing COVID-19 is also not convincing. Although pre-clinical results have been promising, these results have not been supported by clinical findings [25]. Further, postexposure therapy with HCQ did not prevent SARS-CoV-2 infection or symptomatic COVID-19 in healthy persons exposed to a PCR-positive case patient [26,27]. Several trials showed no significant effect of HCQ on clinical outcomes and on the risk of acquiring COVID-19 [28]. Thus, no recommendation can be given so far.

Corticosteroids

Corticosteroids were largely used during SARS-CoV and MERS-CoV epidemics [4]. The ability of corticosteroid treatment to downregulate systemic and pulmonary inflammation-coagulation-fibroproliferation has been proven in ARDS [5,6]. It was shown that suppressing hyperinflammation with corticosteroids (dexamethasone at a dose of 6 mg once daily) is efficacious at reducing mortality, with the greatest benefit among those requiring mechanical ventilation [29]. Dexamethasone thus could be considered for ambulatory treatment. On the other hand, some authors discuss use of corticosteroids should be limited to specific co-morbidities [13,30] and it must be stated that dexamethasone is the corticosteroid associated with greater suppression of the adrenal gland.

Early administration of inhaled budesonide turbohaler at a dose of 800 μg per actuation twice a day reduced the likelihood of needing urgent medical care and reduced time to recovery after early COVID-19, when given within 7 days of the onset of mild COVID-19 symptoms [31]. This regime might also be interesting for daily practice.

In one of the largest SARS-CoV-2 studies, after adjustment for possible confounders, methylprednisolone 80 mg/day was safe and decreased the risk for death significantly [32]. In a large Italian study, methylprednisolone 80 mg for 9 days followed by tapering based on improvement in predefined laboratory parameters significantly improved disease regression [33]. Similar results were seen in a Spanish semi-randomized study with methylprednisolone (3 days each, 80 mg, and 40 mg, respectively) [34]. Another potential dosing scheme for outpatients starting on day 5 or the onset of respiratory symptoms is prednisone 1 mg/kg given daily for 5 days with or without a subsequent taper [35].

Anticoagulation

An important clinical question is whether anti-coagulant therapy can improve the outcomes of COVID-19 patients as incidences of macro and micro-vascular thrombosis in multiple organs are high [9]. Low-molecular weight heparin (LMWH) in prophylactic dose might be associated with a mortality benefit in critically ill patients [36]. But does it offer benefit in outpatient care? As both prophylactic and therapeutic anticoagulation are associated with an absolute decrease of in-hospital mortality and intubation [37], the use of "intermediate" dose thromboprophylaxis, e.g., weight-based prophylaxis with 0.5 mg/kg twice daily of low-molecular weight heparin (LMWH) should be discussed if no contraindication exists [38]. This regimen might be beneficial for outpatients with severe risk of thrombosis due to reduced mobility while illness.

Adjuvant therapy

Various drugs have been considered to have beneficial effects as adjuvant therapy. It is focused on the most promising therapeutics.

Tramadol, a commonly prescribed analgesic drug for treatment of moderate to severe pain might have possible beneficial effects against SARS-CoV-2 infection. The anti-inflammatory effect may help to suppress the COVID-19 related cytokine storm through decreasing interleukin (IL)-6, tumor necrosis factor-alpha (TNF-α), and C-reactive protein (CRP) [39].

Two retrospective studies have demonstrated a strong association of statin use in COVID-19 patients with survival [40,41]. Though they were done in-hospital, a positive effect on vascular system and anti-inflammatory advantages may exist as well for outpatient care [42].

Free thiamine is passively absorbed and converted to active vitamin B1. Multiple roles of thiamine exist, it is also a key co-factor for pyruvate dehydrogenase, without which pyruvate would be converted to lactate as opposed to acetyl-coenzyme A [43]. During critical illness as COVID-19, the prevalence of thiamine deficiency is in 10-20% upon admission and can increase, suggesting rapid depletion of this vitamin [44]. Thiamine can be found in pork, fish, seeds, nuts, beans, green peas, tofu, brown rice, squash, asparagus, and seafood [45]. Dietary intake should be ensured, oral supplementation can be considered, when plasma levels are low. The World Health Organization recommends daily oral doses of 10 mg thiamin for a week, followed by 3–5 mg/daily for at least 6 weeks, to treat mild thiamin deficiency [46].

Supplements

Several substances may be considered because of potential positive preventive effects. In the prophylaxis of COVID-19, Zinc likely has an important role in the treatment of the early symptomatic phase, and in limiting the immune dysregulation and associated cytokine storm in the pulmonary phase [47]. Zinc has antioxidant, anti-inflammatory, immunomodulatory, and antiviral activities and might protect the body's cells and tissues from viral infection [48]. Meta-analyses of RCTS support these findings and have demonstrated that Zinc lozenges at a dose of ≥ 75mg/day (elemental zinc) administered within 24 hours of onset of symptoms and taken for at least 5 days significantly reduced duration of common cold symptoms and use of antibiotics [49].

A prophylactic role of Vitamin D supplementation in COVID-19 is also discussed [9]. It has been shown that SARS-CoV-2 positive tests were associated with low Vitamin D levels [50]. But a relationship between low serum 25(OH)D levels and COVID-19 related health outcomes was not found to be statistically significant. Nevertheless, calcifediol supplementation may have a protective effect on COVID-19 [51]. Regular supplementation with vitamin D potentially decreases the risk of acute respiratory tract infections, especially in patients with severe vitamin D deficiency [52]. Vitamin D may enhance corticosteroid effect when co-administered, like the synergistic effects of corticosteroids with Vitamin C [9,53].

Ascorbic acid (AA) targets multiple molecules and biological pathways involved in inflammatory states such as sepsis and ARDS. It is one of the most potent and important antioxidants in mammals with pleiotropic modes of action [54]. Most studies involved AA as intravenous therapy in Intensive Care Unit patients. As AA showed significant impact on outcomes in the treatment of COVID respiratory failure along with an impeccable safety profile and low cost [9]. Preventive oral intake might be useful at a dose of 150-200 mg per day [55]. Ongoing COVID-19 clinical trials will show if any of these supplements might possible candidates for outpatient treatment. So far, no general recommendation can be given as no single substance has shown to have exclusive preventive potential. Patients should not rely on dietary supplements to prevent or treat COVID-19.

Therapeutic application of endolysosomes based inhibitors or targets

Endolysosome-based therapeutic strategies might restrict SARS-CoV-2 infection. Entry of SARS-CoV-2 into endosomes and its release from endolysosomes play an important role in process of infection. Coronaviruses deliver their genome at replication sites without initiating host detection and immunological responses [56]. Endolysosome de-acidification possibly restricts replication of SARS-CoV-2 because acidic conditions are necessary for SARS-CoV-2 to enter into and be released from host cells [57]. Naturally existing compounds (phytochemicals) might provide therapeutic relief against COVID-19 through their actions on endolysosomes and mTOR signaling pathways as the greater endolysosome pathway may be target [58]. High-risk patients are discussed to benefit from strategies designed to increase levels of 17β-estradiol (by consuming estrogen pills and 17β-estradiol-enriched herbs) [59].

17β-estradiol might decrease SARS-CoV-2 infection by controlling RAAS, suppressing inflammatory storms, inducing anti-viral immune responses, and enhancing the virus' degradation in endolysosomes by promoting the fusion of endosomes and lysosomes [60]. Further investigation is necessary to prove implications of these therapeutic strategies in General Practice.

Natural compounds

The consumption of herbal medicine might improve the immune response. Possible products are *Allium sativum, Camellia sinensis, Zingiber officinale, Nigella sativa, Echinacea spp. Hypericum perforatum, and Glycyrrhiza glabra, Scutellaria baicalensis* [61]. Different types of terpenoids show promising effects in viral replication inhibition, additionally, some alkaloid structures such as homoharringtonine, lycorine, and emetine have strong anti-coronavirus effects. Pytochemicals may have anti-inflammatory, anti-oxidant, and anti-viral properties. These properties might play protective roles in blocking SARS-CoV-2 replication by enhancing

endolysosome acidification, increasing autophagy, and inhibiting mTOR-signaling pathways [58]. Polyamines, as spermidine and spermine, both inhibited SARS-CoV-2 infection and appeared to do so by inducing viral degradation in endolysosomes [62]. Resveratrol is a polyphenol with antioxidant and anti-inflammatory properties and has been found to protect against oxidative damage in high-risk conditions like Middle East Respiratory Syndrome-coronavirus (MERS-CoV) suggesting efficacy against SARS-CoV-2 [63]. Phytoestrogens are natural compounds found in plants such as tofu and sesame seeds [64]. In summary, several natural compounds have shown promise in suppressing SARS-CoV-2 infection in humans, but these compounds may be toxic at higher concentrations and doses [65]. More work is necessary to have confidence that phytochemicals can provide therapeutic benefit against SARS-CoV-2 infection. At this point of time no strong recommendation can be given for daily routine.

Conclusion

Regarding meta-analysis studies about the COVID ambulatory care, little or no suggestion of benefit for most treatments and outcomes in both non-severe and severe COVID-19 was found [66]. Much more progress is necessary to find causal therapies in this devastating pandemic. Aside from preventive actions and vaccination, most important strategies in therapy are symptomatic supportive treatment along with anti-inflammatory therapies including corticosteroids [67]. Most important, supportive care including supplemental oxygen, monitoring, and telemedicine should be available. It is made clear that the decision to give or not give drugs is always the responsibility of the prescriber with many other factors having to be considered such as age and electrolyte imbalance [68]. Awareness of drug-drug interactions in COVID-19 treatment in patients with comorbidities is essential. Prohibition of severe COVID-19 cases requires early identification and effective treatment in outpatient care. Due to great range of clinical severity from asymptomatic to fatal in COVID-19, it is necessary to strengthen outpatient care. Some practical strategies have been given based on pathophysiological principles. The aim must be reduction in hospitalization and death. General preventive actions should strongly be supported: taking care of social distancing, wearing face mask, and measures of hygienics as well as vaccination against SARS-CoV-2 for as many people as possible. At this point of pandemic, there is no alternative of action.

Conflicts of interest/Competing interests

There are no conflicts of interest to declare.

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