

Updates on Acyclovir in the Management of Respiratory Infectious Diseases with Special Reference to COVID-19

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Abstract: The COVID-19 pandemic greatly accelerated attempts to produce treatment approaches that specifically target the SARS-CoV-2 (coronavirus), which results in acute respiratory distress. Thousands of individuals have been recruited in clinical trials for hundreds of potential drugs, but for now, there aren't many approved drugs to treat COVID-19. This review discusses the pathogenesis, the epidemiology of COVID-19 in India and worldwide, the role of acyclovir in treating COVID-19, its mechanisms of action, and other medicines shown to combat COVID-19. We also discuss the epidemiology, SARS-CoV-2 targeted inflammatory and immune responses, coagulation, and available treatments for acute respiratory infections and COVID-19. In addition to these issues, their view discusses lessons learned on drug repurposing methods, platform trial design, and targets or treatments effective against coronavirus, which can be used to develop medicines against COVID-19 and other respiratory infections.

Keywords: COVID-19; SARS-CoV-2; acyclovir; coronavirus; acute respiratory syndrome.

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1. Introduction

Respiratory infectious diseases are a serious global health threat, with millions of individuals worldwide affected every year by transmissible respiratory diseases[1]. The majority of acute respiratory infections worldwide occur in the upper airways, but there are also many cases of lower respiratory tract infections, such as pneumonia and bronchiolitis. Respiratory syncytial virus (RSV) and influenza viruses, as well as bacteria such as *Streptococcus pneumoniae* and *Haemophilus influenzae*, are considered primary etiologic agents in these respiratory diseases. Children's bronchiolitis and moderate upper and middle respiratory tract infections in children are also significantly influenced by viruses. Common viruses associated with respiratory tract infections include influenza viruses, RSV, metapneumoviruses, parainfluenzaviruses, adenoviruses, coronaviruses, and bocaviruses [2].

Clinical presentations of viral respiratory illnesses range from asymptomatic cases to infections that may or may not be lethal. While certain viruses, like the adenovirus, rhinovirus, and coronavirus, are associated with infections mostly in the upper respiratory tract, others,

including RSV, parainfluenza, influenza, metapneumovirus, and adenovirus, cause infections of the lower respiratory airways of varying degrees of severity. Every respiratory virus can impair one or more levels of the respiratory system and cause clinical and subclinical illnesses, although some viruses target specific levels of the respiratory system, while others do not [3].

Coronavirus SARS-CoV-2 belongs to the *Coronaviridae* family, which is classified into four groups: *alpha*, *beta*, *gamma*, and *delta* coronaviruses. Coronaviruses impact the respiratory system and are single-stranded RNA viruses [4]. SARS-CoV-2 is one of the most recent viruses to have spread globally, and in March 2020, following the rapid global spread of respiratory illness after early reports of an epidemic in China in December 2019, the WHO declared the outbreak of COVID-19 a pandemic [5,6]. SARS-CoV-2 is transmitted through respiratory droplets, with infected patients often showing symptoms 2 to 12 days after infection [7]. The symptoms of the disease include sore throat, high fever, pneumonia, cough, dyspnea, and respiratory distress syndrome [4]. Other symptoms involve headache, myalgia, fatigue, nausea, diarrhea, anosmia, vomiting, and impaired sense of smell and taste. Although COVID-19 mostly affects the respiratory system, its clinical presentations show that it can also affect other parts of the body, impacting the brain and leading to encephalopathy, delirium, or seizures. COVID-19 illness has also been associated with arrhythmias, myocarditis, congestive heart failure, and acute coronary syndrome of the heart [8]. Systemic disorders can also lead to kidney damage. Skin abnormalities have also been documented, including patchy erythematous rashes [8]. In COVID-19, the respiratory tract epithelium becomes infected, leading to uncontrolled viral replication in epithelial cells. A viral infection is typically not completely countered and cleared by an antibody response, especially when the virus has become established in the host cells [9]. Thus, SARS-CoV-2 appears to trigger a variety of illnesses in people, ranging from asymptomatic to serious, including lethal health issues. 80% of those infected either show no symptoms at all or very minor ones [8]. The key features of COVID-19 are described in Figure 1.

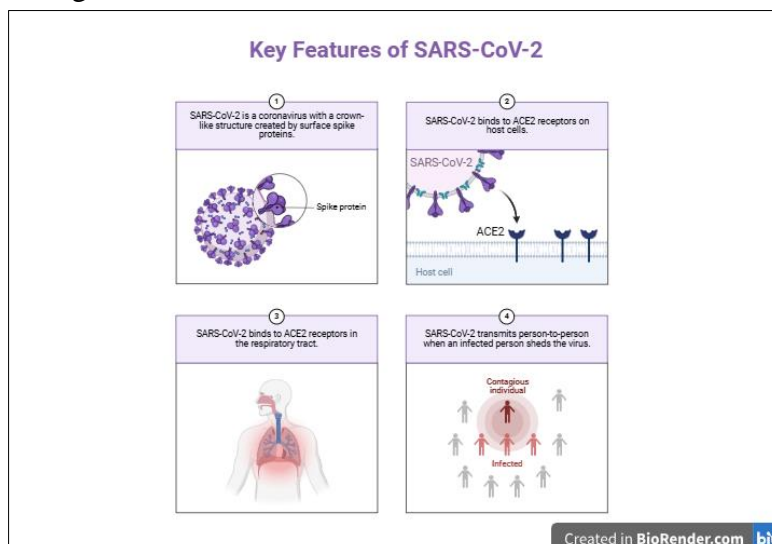


Figure1. Key features of the mechanism of SARS-CoV-2 transmission.

Acyclovir is an antiviral drug that inhibits DNA polymerase competitively by phosphorylation of the active agent, and it is now also being suggested that acyclovir works by blocking IL-12 (interleukin) from attaching to the IL-12 receptor [10]. By addressing elevated serum cytokine levels and preventing the cytokine storm, acyclovir holds promise for the treatment of COVID-19. The FDA has approved acyclovir for the treatment of varicella, herpes

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zoster, genital herpes, and herpes simplex virus encephalitis, and has also been prescribed off-label to treat COVID-19, where small-scale studies have demonstrated its efficacy, safety, and affordability [8].

2. Epidemiology

With some exceptions, most respiratory viruses are spread by person-to-person contact via inhalation of small or large droplets, fomites, small-particle aerosols, and self-inoculation from contaminated hands. In the early stages of the disease, patients are the most infectious. In semi-closed communities, such as schools, hospitals, and nursing homes, the incidence of secondary attacks may be particularly high. Transmission can be prevented to some extent by frequent washing of hands and covering the mouth when coughing or sneezing, while the preventive effects of both mask-wearing, social distancing, and isolation, or “lockdown”, as during the COVID-19 pandemic, are disputed. In temperate climates, several virus-associated illnesses show substantial seasonal fluctuations, with influenza and RSV outbreaks usually occurring in the winter [2]. According to data from the National Health Portal of India, in 2019, 3,740 respiratory infection-related deaths and 41,996,260 cases occurred in India 2018. Among infectious diseases, 69% of acute respiratory infection cases occurred before the emergence of SARS-CoV-2 in 2019. During the COVID-19 pandemic, millions of people worldwide were infected with SARS-CoV-2. Figure 2 shows an analysis comparing the prevalence rates of viral infections in India with those in other countries over the period from 1970 to 2020 [11].

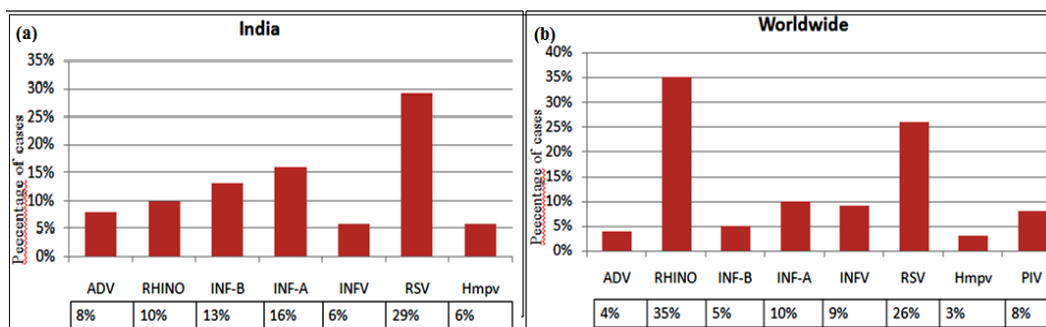


Figure 2. Cases of viral infections. Prevalence rates of viral infections (a) in India; (b) worldwide in the years 1970-2020.

The coronavirus family is a large group that affects both humans and a wide range of animal species, including cats and bats, and most people are infected with (some of) these viruses at some point in their lives. Common human coronaviruses commonly cause the common cold and other upper respiratory tract infections (URTIs), and while some varieties cause mild symptoms similar to a light cold or asymptomatic flu, COVID-19 was linked very early in the developing pandemic to significant mortality rates, particularly in patients with chronic co-morbidity conditions, including diabetes and heart disease [12].

As mentioned above, coronaviruses are divided into 4 main categories: alpha, beta, gamma, delta, and omicron [11,13,15]. The alpha variant, first reported in the UK and designated B.1.1.7 [13, 15], is associated with increased transmission and increased severity of infection [14]. The beta variant, designated B. 1.351, was first reported in South Africa and is associated with increased transmission and reinfection rates [14]. The gamma variant, designated P.1, was first detected in Brazil and was associated with an increased rate of hospital admissions [14]. The Delta variant, designated B.1.617.2, was first reported in India and was responsible for the second wave of coronavirus in April 2021. Initially, it was known as a

variant of interest [15]. The new omicron variant was first identified in South Africa and designated B.1.1.529. Because the spike (S) protein of this virus has undergone more than 30 mutations, it was soon identified as a variant of concern [15]. The first human coronaviruses were identified in the mid-1960s [2], and since then, a range of varieties that impact people all around the world, such as HKU1, NL63, 229E, and OC43, have been identified, alongside many others. HKU1 and OC43 are β -coronaviruses, whereas NL63 and 229E are α -coronaviruses [12], and all these coronaviruses typically cause mild to severe URTIs with symptoms similar to those of the common cold. Notably, some coronaviruses associated with transmissible diseases among animals can adapt and mutate, promoting the coevolution of coronaviruses that may eventually give rise to novel human coronaviruses [16]. In line with current theories and models, COVID-19 was initially thought to be a zoonotic illness that originated in bats and underwent multiple cross-species transmissions, first to pangolins and then to humans. One or more zoonotic transmission incidents in Wuhan's wet market *also* appeared to be the catalyst for the outbreak [17].

The first indications of these epidemiological connections came from a number of documented cases of acute respiratory distress, whose radiological characteristics were unique. For example, the first chest images showed consolidation and multifocal opacities in the airways in 70 to 80% of coronavirus-infected patients [18]. Since then, more questions have been raised concerning the zoonotic origin of SARS-CoV-2, and there are no definitive answers yet concerning the origins (or evolution) of this virus and its mutant variants.

3. Respiratory Tract Infection Due to Viruses

Respiratory viruses are among the most prevalent disease-causing agents in humans and have a major impact on morbidity and mortality, especially among youngsters, throughout the world [19,20]. Acute respiratory infections are thought to be a contributing factor in around one-fifth of all pediatric mortality globally, with underprivileged populations in tropical areas being particularly exposed compared to those in temperate areas. HPIV, HRSV, HRV, ADV, HBoV, and HMPV are common viruses that cause respiratory tract infections, while SARS-CoV and H5N1 have only recently been identified as serious public health hazards due to widespread, eventually global outbreaks of disease [21].

Respiratory tract infections develop when a virus penetrates respiratory mucosal cells following inhalation of viral particles or *via* direct transfer via contaminated hands that come into contact with the mucosal layers of the nose and eyes. Generally, it is assumed that infected people release the virus into the air through droplets produced when they sneeze and cough, allowing people in the vicinity to inhale virus-containing droplets.

Table1. Common viral respiratory tract infections.

Virus	Disease
HPIV(humanparainfluenzavirus)	URI, bronchitis, bronchiolitis, pneumonia
HRSV(humanrespiratorysyncytialvirus)	URI, bronchitis, bronchiolitis, pneumonia
HRV(humanrhinovirus)	URI, COPD, and asthma
SARS-CoV(severeacutererespiratorysyndrome)	SARS
ADV(adenovirus)	bronchitis, URI, pneumonia
HBoV(humanbocavirus)	bronchitis, bronchiolitis, URI, asthma, pneumonia
HMPV	bronchitis, URI, pneumonia

When someone comes into contact with a surface contaminated with virus-containing droplets and then touches their nose, lips, mouth, or eyes, they may pick up the infection. Small droplet nuclei (less than 5 μ m) that remain in the air for extended periods and enter the lower

respiratory tract are another way viruses are transmitted through the air [22]. Some common respiratory diseases and the viruses associated with them are described in Table 1.

4. Prevalence and Diagnosis of Respiratory Viruses

Since various respiratory viral infections share similar symptoms, it is nearly impossible to diagnose the specific virus based solely on symptoms. The only method for confirming a virus infection diagnosis is nucleic acid sequence detection to determine whether a biological sample contains viruses and, from there, which virus the sample contains. The most common diagnostic technique is PCR (polymerase chain reaction) and its variations, which, after specific primer and probe design and optimization in the lab, are performed using either a single primer set or a multiplex format. Although they are in use, immunofluorescence tests have drawbacks, such as low sensitivity. Other challenges with confirmation by culture include access to advanced cell culture facilities and secure containment, which can be difficult in many regions of the world. In response to the epidemic nature of the viral disease, numerous nations have implemented influenza surveillance and multiplex real-time PCR assays to identify circulating viruses and outbreaks and estimate disease burden in the population [11, 23].

5. SARS-CoV-2–Structure and Epidemic Potential

SARS-CoV-2 is an encapsulated single-stranded RNA virus. The genome of SARS-CoV-2 is among the largest of RNA viruses, measuring approximately 29.9 kb. Four structural proteins (spike, nucleocapsid, membrane, and envelope) (Figure 3), 16 non-structural proteins (NSP1-NSP16), and 9 accessory proteins are encoded by it (Figure 4). Overall, the SARS-CoV-2 life cycle comprises entry, proteolytic processing, RNA synthesis, and assembly [24]. The life cycle of the COVID-19 virus is depicted in Figure 5.

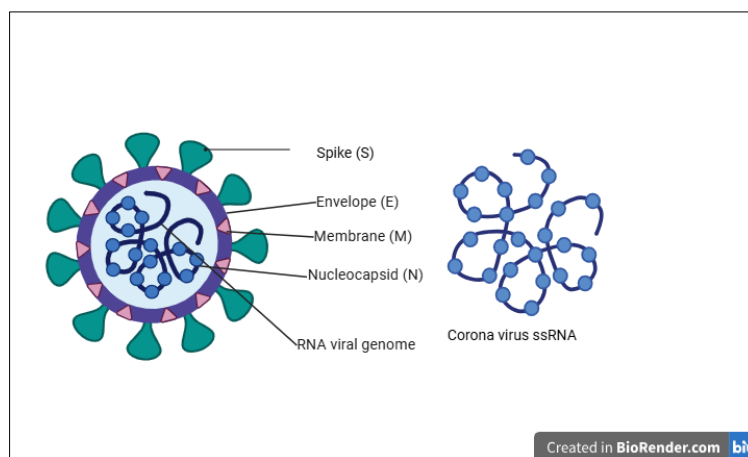


Figure 3. Human coronavirus structure.

Figure 4. Coronavirus RNA genome. The genome of the coronavirus is a positive-sense RNA molecule, and it is organized into several regions, each of which serves specific functions in the virus's life cycle. The general structure of the coronavirus genome includes the following elements : (1) 5' cap and leader sequence: The genome begins with a 5' cap structure, similar to the host cell's mRNAs. A leader sequence follows this cap and is important in RNA synthesis as well as the translation of viruses. (2) Open reading frames (ORFs): The genome contains several open reading frames that encode different proteins. Two large polyproteins encoded by ORFs are expressed as pp1a and pp1ab, which subsequently act on individual non-structural proteins. (3) Replicase gene: The replicase gene is encoded by the large polyproteins and plays an important role in replication as well as transcription of the viral RNA. Various non-structural proteins are included that form the complex of viral

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replicase and transcriptase enzymes. (4) Structural proteins: The structural proteins are encoded by the genome, which is required for the assembly of new virus particles. These include the spike, envelope, nucleocapsid, and membrane proteins. (5) Other accessory proteins: a set of accessory proteins with diverse functions is also encoded by coronaviruses. These proteins are important for enhancing viral replication and the host immune response. (6) 3' UTR (Untranslated Region): The 3' end of the genome contains a non-coding region, including the 3' UTR, which is important for viral RNA synthesis and packaging.

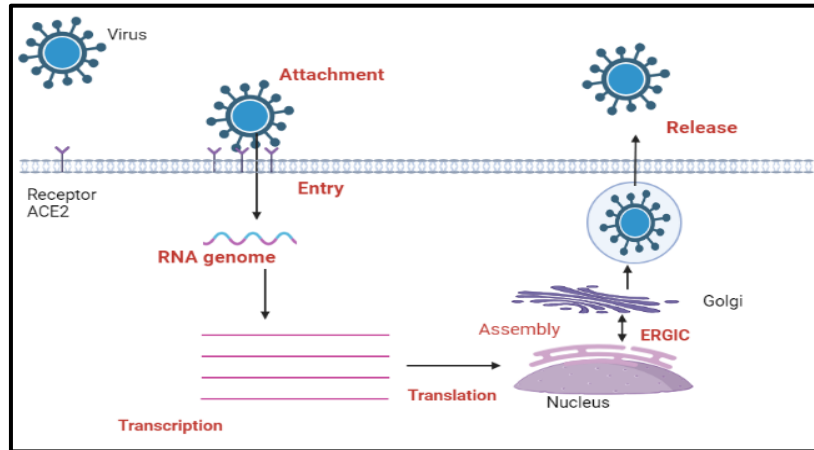


Figure 5. COVID-19 virus replication life cycle. SARS-CoV-2 replication involves several stages in the virus's life cycle. The illustration above shows a simplified overview: Attachment and Entry. The angiotensin-converting enzyme 2 (ACE2) receptor on the host cell's surface is bound by the spike protein present in the virus. The virus is then endocytosed into the host cell. Release of Viral RNA: The virus releases its RNA into the host cell's cytoplasm once it has entered the cell. Translation and Replication: The host cell's machinery translates the viral RNA into viral polyproteins. The viral host then cleaves these polyproteins into individual viral proteins. To produce additional viral RNA genomes, the enzyme viral RNA replicase transcribes the viral RNA. Assembly of Viral Components: New viral RNA genomes and viral proteins are transported to the endoplasmic reticulum (ER) and Golgi apparatus for assembly. Viral components are assembled into new virions. Maturation and Release: The new virions are transported through the secretory pathway. The viruses are then released from the host cell by exocytosis, often causing cell damage or death. Understanding the details of the virus's replication cycle is crucial for developing antiviral drugs and vaccines. Disrupting any of these stages in the life cycle could be a potential target for therapeutic intervention.

The epidemic potential, or ability, of a virus to spread in a population is represented by a number called the reproductive number; the higher this number, the more serious the epidemiological potential of the infection [25]. The estimated reproduction rate of some viruses is summarized in Table 2.

Table2. The estimated reproduction rate of some viruses.

Viruses	R ₀ estimates (average)
Influenza	1-3
SARS	2-5
HIV/AIDS	2-5
Smallpox	5-7
Rhinovirus(cold)	5-7
Chickenpox	8-9
Whooping cough (Pertussis)	12-17

Preliminary epidemiological data indicate that SARS-CoV-2 is extremely contagious, with an effective reproductive number (R₀) of roughly 2.2 [26]. It also appears that COVID-19 is associated with significantly higher mortality than influenza. However, the exact figures are uncertain (due to variations in weighing, e.g., the impact of pre-existing conditions on mortality).

6. Pathological Effects of SARS-CoV-2 Infection on Alveolar Epithelial Cells

Endothelial cells may become infected with SARS-CoV-2 from the alveolar or luminal interstitial side. The infection may cause endothelial cytokine production that increases capillary permeability, facilitates neutrophil and monocyte adherence and extravasation into the alveolar interstitium, and causes endothelial cell dysfunction. It leads to micro- and macrovascular injury to cells [27].

Neutrophils and macrophages are activated by PAMPs (pathogen-associated molecular patterns) and DAMPs (damage-associated molecular patterns), which trigger the secretion of a variety of cytokines, procoagulants, and complement. These substances are said to be involved in the attack and clearance of viruses, but they can also cause additional vascular damage, increasing the risk of thrombosis. Numerous elements could support a prothrombotic environment and encourage the development of intravascular thrombi: (1) Complement and NETs (neutrophil extracellular traps) are secreted by neutrophils, which promote platelet aggregation. (2) The coagulation cascade is stimulated, and fibrin clot formation is increased by endothelial cells and macrophages (by secreting tissue factor) in response to cytokine stimulation. (3) Overactivation of angiotensin receptors and ACE (angiotensin-converting enzyme) by the virus causes reduced plasmin activation, fibrinolysis and increases the synthesis of PAI1 (plasminogen activator inhibitor 1)(Figure 6) [28].

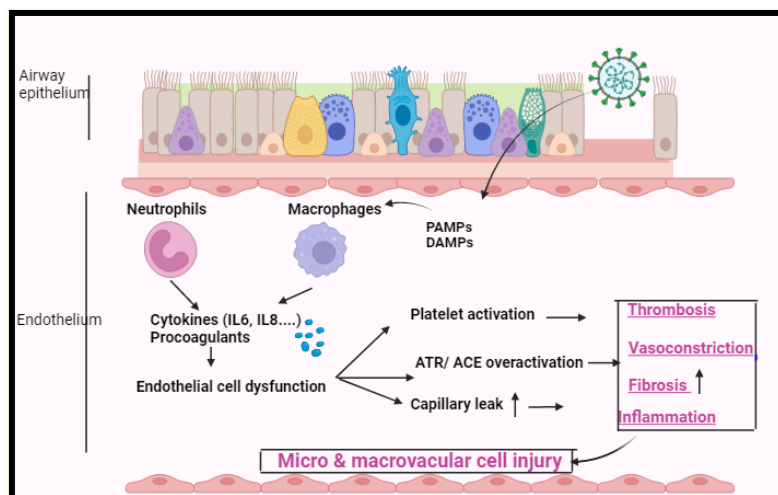


Figure6. Pathological consequences of vascular endothelial injury by coronavirus-2 (SARS-CoV-2) infection.

The body's immune system responds aggressively to a COVID-19 infection, to the point of malfunctioning. These reactions are frequently linked to serious clinical symptoms such as acute respiratory distress syndrome, systemic inflammation, and multi-organ damage [29]. Many investigational medications and a wide variety of commercially available immunomodulators and anticoagulants have been repurposed to reduce aggressive immune responses in COVID-19 patients [30]. Here, we will present some of the drugs that have been used and prescribed off-label to treat the most severe cases of COVID-19 illness.

7. Available Treatments

As yet, there are no known effective, all-around treatments for SARS-CoV-19 infections, and as a result, the primary goals of disease management are focused on symptom treatment, supportive therapy, and prevention of respiratory and other organ failure. The course

of treatment consists of targeted therapies, such as antiviral medications, and supportive management of any pre-existing conditions or complications, like advanced organ support [31].

In addition, it is important to ensure patient isolation to prevent the spread of infection to other patients, medical professionals, and family members. Isolating infected people, both symptomatic and asymptomatic, as well as anybody who may have come into contact with them, requires quarantine measures or lockdown of society, which, while widely implemented, have come under increased scrutiny [32].

The development of drugs specifically to target SARS-CoV-2 is focused on agents that may interrupt the life-cycle of the virus at critical phases, such as spike inhibitors, which act on the entry mechanism, protease inhibitors, which act on proteolytic processing, NSP12 to NSP16 inhibitors of RNA synthesis, and nucleocapsid inhibitors acting on assemblies of the virus (Table 3) [24].

Studies have shown that chloroquine exhibits activity against coronavirus *in vitro* [33,34], and this activity has been confirmed in *in vivo* studies, which have shown that administration of chloroquine to treat pneumonia from COVID-19 infection may increase treatment success, enhance patient outcomes, and reduce the length of hospital stay [35]. The 4-aminoquinolone, generally used as an antimalarial and anti-inflammatory drug, has broad antiviral activity. Ritonavir, or lopinavir, which is generally used to treat HIV-1 infection, became prominent in 2003 during the SARS pandemic, when its *in vitro* efficacy against the SARS-CoV virus was documented. The neuraminidase inhibitor oseltamivir is a key medication in the treatment of influenza. Because neuraminidase is absent, it has not been demonstrated to have activity against CoVs and is therefore unlikely to be beneficial. An innovative medication called Remdesivir, an RNA polymerase inhibitor and adenosine analog, was developed to treat Ebola virus infection. It is regarded as a potential medication because of its safety profile in Ebola studies, broad-spectrum antiviral activity, and *in vitro* activity against SARS-CoV-2. An RNA polymerase inhibitor called favipiravir has been used to treat COVID-19 in China and is currently being investigated in clinical trials for mild SARS-CoV-2 disease and as an adjuvant for moderate and severe illnesses [31]. For outpatients with mild to moderate COVID-19, early antiviral medication is essential to reduce the risk of developing severe COVID-19. Unfortunately, most currently marketed antiviral medications, aside from oral ritonavir, nirmatrelvir, and molnupiravir, are administered by injection, often in infusion centers and hospitals, making them difficult to administer in outpatient and resource-constrained settings. In addition to antiviral medications, over-the-counter medications such as paracetamol (acetaminophen) can effectively manage symptoms like fever associated with COVID-19; however, they are not helpful in eliminating coronaviruses [36]. Treatment with immunomodulators and anti-inflammatory medications is not recommended during the early stages of COVID-19 due to increasing viral loads and immune response suppression. However, combining antiviral drugs with supportive therapies such as anticoagulants, immunomodulators, and anti-inflammatory medications may provide synergistic benefits for hospitalized patients with severe or critical COVID-19. Hospitalized individuals who require oxygen assistance respond well to a combination of remdesivir and dexamethasone [37].

7.1. Systemic corticosteroids.

Corticosteroids are inexpensive, widely accessible medications that inhibit the immune system and reduce inflammation in autoimmune and other inflammatory diseases. Hydrocortisone and dexamethasone are now advised [24, 38] for the treatment of COVID-19

in patients with oxygen support. The first glucocorticoid that was shown to have a positive therapeutic effect on in-patients with severe COVID-19 is dexamethasone. For example, research conducted shortly after the COVID-19 outbreak demonstrated that dexamethasone administration decreases the 28-day mortality rate among COVID-19 in-patients requiring respiratory support. Using dexamethasone alone or in combination with tocilizumab and antivirals has also proven helpful in the treatment of COVID-19 patients (critical or moderate to severe cases) [24].

7.2. Cytokine antagonists

Blocking pro-inflammatory cytokines, such as IL-6, at the receptor site may also be a helpful strategy for treating COVID-19 patients to reduce inflammatory reactions and decrease cytokine production. Tocilizumab is one of the IL-6 receptor antagonists that reduce inflammatory responses and improve clinical outcomes in COVID-19 in-patients [24,39]. Based on a clinical trial study, tocilizumab was added to usual therapy (glucocorticoids in 82% of instances) for COVID-19 in-patients who had baseline systemic inflammation and hypoxia, reducing the number of patients receiving invasive mechanical ventilation, leading to an overall reduction in mortality and an increase in discharge from hospital care by 28 days (NCT04381936) [24,39].

7.3. Janus kinase inhibitors.

The Janus kinases, which include JAK1, JAK2, and JAK3, are a family of receptor-mediated cytosolic tyrosine protein kinases. In the presence of interferons, the JAK-STAT signaling pathways and transcriptional regulation are activated, thereby influencing the immune system, exogenous cytokines, and growth factors [24,40]. Since Janus kinase inhibitors like tofacitinib and baricitinib are already licensed to treat immune-mediated inflammatory conditions, including rheumatoid arthritis, they can be easily repurposed as medications to lower inflammation and suppress immunological dysregulation linked to COVID-19. However, JAK inhibitors alone are not enough to cure COVID-19 [24].

7.4. Interferon treatment.

It is recognized that type I interferons play crucial roles in the immune responses that protect the body from viral infections. Examples of these interferons are interferon- α (IFN α) and IFN β . Early administration of the combination of remdesivir and IFN β -1b can potentially decrease viral transmission and hospital stays in high-risk individuals, as indicated by a Phase III study showing that Peg-IFN λ -1a in outpatients reduced ER visits or hospital admissions among COVID patients [41].

7.5. Anticoagulant.

Many COVID-19 patients, particularly those with severe pre-existing conditions, are at risk for venous thromboembolism, associated with reduced clinical outcomes and increased risk of death, also in COVID-19 patients. Anticoagulants, like heparin, are commonly administered to reduce the risk of thromboembolism. Still, the overall effect of heparin depends on the severity of the disease, the patient's overall condition, and when treatment is started. The use of low-molecular-weight heparin, as opposed to general care, was associated with improved hospital discharge and a lower need for respiratory or cardiovascular organ support

in a large-scale randomized trial involving 2,219 patients with low-to-moderate COVID-19 illness. In line with this, the clinical use of heparin to reduce the risk of thromboembolism in COVID-19 patients who are not pregnant or in the intensive care unit is widely accepted[42].

7.6. Anti-inflammatory drugs.

NSAIDs may be administered to COVID-19 patients as adjuvant treatment to reduce hyperinflammation induced by SARS-CoV-2, possibly lowering the risk of developing severe COVID-19. Topotecan, an FDA-approved anticancer drug, inhibits human topoisomerase in animal models, thereby diminishing SARS-CoV-2-induced inflammation. It is being studied for a phase I trial (NCT05083000). Vilobelimab, an anti-C5a mAb, inhibits C5a-C5aR1 signaling to reduce coagulation and inflammation, and decreases mortality among COVID-19 in-patients on mechanical ventilation, as found in the phase III PANAMO trial. In April 2023, the FDA approved the use of vilobelimab as an emergency treatment for hospitalized COVID-19 patients, provided that the medication was started within 48 hours of oxygen support [43].

Antiviral therapies for significant viruses that cause human respiratory tract infections are listed in Table 3. Most of these result in community-acquired infections. Some of them, like cytomegalovirus, are mostly opportunistic infections that target hosts with impaired immune systems. Nearly every pathogen has been linked to infections in the vulnerable, which could lead to significant morbidity and mortality. Table 4 describes the treatment specifically targeted at SARS-CoV-2 infections.

Table 3. Antiviral drugs target viruses in the human respiratory tract.

Virus	Antiviral drug	Treatment duration	Adultdose
Human adenovirus	Vidarabine	Five days, and the course is repeated if required	10 mg/kg Once daily Intravenous
	Ribavirin	Seven days, so run til the virus is eliminated	Loading dose of 33 mg/kg Followed by 16 mg/kg (every 6h) for 4 days Followed by 8 mg/kg (every 8h) for 3 days Intravenous
	Cidofovir	Until the virus is eliminated	Initially, 5 mg/kg once weekly for 2 weeks, followed by 5mg/kg once every two weeks Intravenous
Varicella zoster virus	Acyclovir	10–21 days	10 mg/kg every 8h Intravenous
Herpes simplex viruses	Acyclovir	10 days.	10 mg/kg every 8h Intravenous
	Cidofovir		5 mg/kg Once a week Intravenous
Human respiratory syncytial viruses	Ribavirin	Immunocompetent patient–7 days.	6 g min 100 mL water over 2hrs, 3 times a day (Aerosol) Loading dose 10 mg/kg Followed by 400 mg and 600 mg, consequently
		Immunocompromised patient: 3 days to over 14 days	Loading dose 33 mg/kg Followed by 16 mg/kg for 4days Followed by 8 mg/kg for 3 days Oral
HPIV (human parainfluenza virus)	Ribavirin	7 days	Loading dose 10 mg/kg on day one and 400 mg 3 times daily Followed by 400 mg Followed by 600 mg Oral Switched to 10mg/kg (every 8hrs) Intravenous
HRV (human rhinovirus)	Ribavirin		Loading dose 10mg/kg on day one and 400mg 3 times daily

Virus	Antiviral drug	Treatment duration	Adultdose
			Followed by 400 mg Followed by 600 mg Oral Switched to 10mg/kg (every 8hrs) Intravenous
Adeno virus	Cidofovir		5mg/kg once weekly for 2 weeks Intravenous
	Vidarabine		10mg/kg per day Intravenous
	Ribavirin		Loading dose 33mg/kg Followed by 16 mg/kg for 4 days Followed by 8mg/kg for 3 days Intravenous
Cytomegalo virus	Acyclovir		500mg/kg, intravenous 800mg oral —q6h

Table 4. Drugs used to specifically target SARS-CoV-2 infections.

Drug name	Mode of action	Eligible patient	Status	Resistance	Route of drug delivery	Type
Remdesivir	RdRp inhibitors	Within 7 days of the onset of symptoms for outpatients or in-patients	FDA approved	Low	Intravenous	Small molecule
Molnupiravir		Outpatients: ≥ 18 years old and ≤ 5 days after the onset of symptoms	Approved in UK	Low	Oral	Small molecule
Ritonavir-Nirmatrelvir	M ^{pro} inhibitors	Outpatients with symptom onset within 5 days	Approved in the EU and UK	Low	Oral	Small molecule
Hydrocortisone	Glucocorticoid	In-patients needed an oxygen supply	COVID-19 guidelines recommended	No	Intravenous	Small molecule
Dexamethasone		In-patients needed an oxygen supply	COVID-19 guidelines recommended	No	Intravenous	Small molecule
Bebtelovimab	Antispike antibodies	Within 7 days of the start of symptoms for outpatients	EUA by the FDA, but paused due to resistance	High	Intravenous	mAb
Etesevimab and Bamlanivimab		Within 10 days of the onset of symptoms for outpatients	EUA in many countries but paused due to resistance	High	Intravenous	MAB
Regdanvimab		Within 7 days of the start of symptoms for outpatients	EUA is available in many countries, but it has been paused due to resistance	High	Intravenous	MAB
Tofacitinib	Janus kinase inhibitors	In-patients needed an oxygen supply	COVID-19 guidelines recommended	No	Oral	Small molecule
Baricitinib		In-patients needed an oxygen supply	COVID-19 guidelines recommended	No	Oral	Small molecule
Heparin (low molecular weight)	Anticoagulants	ICU patients (not pregnant)	COVID-19 guidelines recommended	No	Subcutaneous, Intravenous, or oral	Various
Vilobelimab	Anti-C5a inhibitors	For hospitalized individuals, oxygen assistance	EUA FDA approved	No	Intravenous	MAB

Drug name	Mode of action	Eligible patient	Status	Resistance	Route of drug delivery	Type
		for at least 48 hours				
Sarilumab	Cytokine antagonists	In-patient who needed oxygen support and was receiving systemic corticosteroid	COVID-19 guidelines recommended	No	Intravenous	Anti-IL-6RmAb
Tocilizumab		In-patient who needed oxygen support and was receiving systemic corticosteroid	COVID-19 guidelines recommended	No	Intravenous	Anti-IL-6R mAb

8. Role of Acyclovir in COVID-19

Acyclovir is a well-known antiviral drug that has been approved for the treatment of infections caused by the zoster and herpes viruses. A clinical research study has been published, demonstrating the potential of acyclovir for the treatment of SARS-CoV-2 infection [44]. The FDA has approved the use of acyclovir to treat varicella, herpes zoster, genital herpes, and herpes simplex virus encephalitis. In small-scale studies, acyclovir has been shown to be effective, safe, and reasonably priced in treating COVID-19 [8]. Acyclovir and other COVID-19 treatment regimens have been successfully used to treat herpes infections and COVID-19 infections concurrently in some cases. Additionally, acyclovir has been suggested as a successful treatment for COVID-19 through several mechanisms, including inhibition of RNA-dependent RNA polymerases (RdRPs), modulation of viral gene expression, and suppression of viral proteases [44].

8.1. Chemistry of acyclovir.

Acyclovir (2-amino-1,9-dihydro-9-[(2-hydroxyethoxy)methyl]-6H-purin-6-one) is a guanine nucleoside analog (Figure 7) and a widely used antiviral drug globally. Due to its minimal cytotoxicity and great selectivity, it is seen as the beginning of a new era in antiviral treatment. It is a powerful and effective herpes virus inhibitor, effective against Epstein-Barr virus and herpes zoster virus, and used to treat genital herpes, recurrent skin infections, immunological deficiencies worsened by chickenpox, and various other infections.

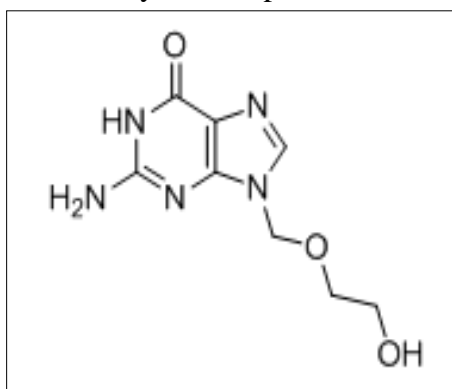


Figure 7. Chemical structure of acyclovir.

8.2. Mechanism of action of acyclovir.

Acyclovir binds to viral DNA, preventing further viral DNA synthesis. Once it is changed by cellular and viral enzymes into acyclovir-triphosphate, it stops the replication of

viral DNA in three ways: by competitive inhibition of viral DNA polymerases, by incorporation and termination of the growing viral chain, and by inactivation of viral DNA polymerases irreversibly. The synthetic purine nucleoside analog acyclovir has exhibited inhibitory effects against both herpes simplex virus types 1 (HSV-1) and 2 (HSV-2), and varicella zoster virus, *in vitro* and *in vivo* (Figure 8) [45].

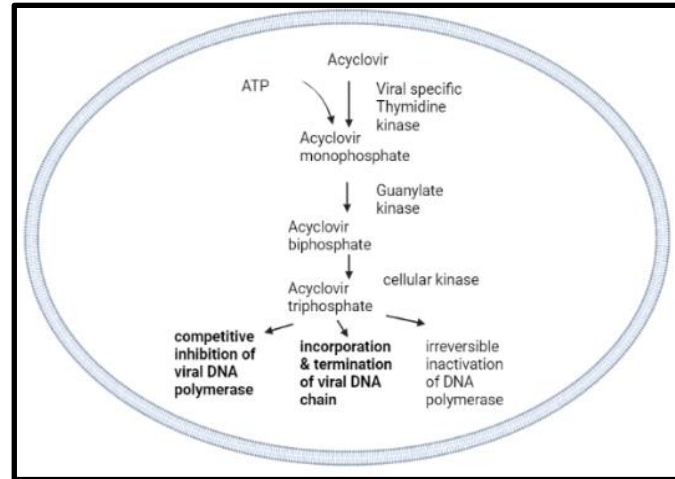


Figure 8. Mechanism of action of acyclovir.

9. Clinical Trials in COVID-19

Over the past three years, thousands of compounds have been assessed in over 10,000 registered clinical studies for COVID-19 [24]. However, many of these trials are duplicates, and the majority do not meet the requirements of clinical trial protocols (such as randomization, double-anonymized, placebo-controlled). There are also conflicting results reported from several small-scale experiments with medications like hydroxychloroquine, which have been controversial and sometimes proved futile. Other challenges have been associated with clinical trial performance, such as travel restrictions and lockdowns, which have impaired international research collaboration and limited clinical trial options.

Large-scale, long-term randomized clinical trials that allow adding new interventions and updating the control group, such as REMAP-CAP, Solidarity, and RECOVERY, employ a single master protocol to evaluate several interventions simultaneously against a shared control group. One of the most successful trials is the ongoing RECOVERY study, launched in March 2020 and involving over 50,000 COVID-19 patients. Its goal is to generate significant data regarding the safety and efficacy of baricitinib, dexamethasone, tocilizumab, and imdevimab casirivimab. Additionally, it has so far demonstrated the ineffectiveness of azithromycin, aspirin, colchicine, ritonavir, dimethyl fumarate, and hydroxychloroquine in COVID-19 patients [24].

10. Case Studies Reported in the Literature

According to the case study of German *et al.*, Patient A experienced a strange symptom of Hyperverbia [8]. This patient was not known for being very chatty before contracting COVID-19, and he was unable to control how quickly he spoke after becoming infected. This uncommon symptom demonstrates the variety of neurological consequences that the COVID-19 virus can cause. Viral encephalopathy was diagnosed as a result of these symptoms and COVID-19 infection. The acyclovir 400 mg three times a day (TID) medication was initiated

in response to this new diagnosis. Patient B was diagnosed with signs of pneumonia on imaging and embolic alterations. His numerous symptoms were in line with viral encephalopathy, which was confirmed by the diagnostic and imaging results. In this case, a series of doctors decided to treat Patient A-D off-label with acyclovir. Acyclovir was administered orally to these patients at BID, TID, and QID. The doctor carefully monitors the patients' development by measuring immunoglobulin titers and the symptoms they describe. The patients reported improvement in symptoms, and consistently declining IgG and IgM immunoglobulin levels were used to determine the treatment's efficacy [8].

A case report of Baker presents clinical cases that were treated with acyclovir. Acyclovir has been used to treat 38 people so far. The four cases that follow demonstrate the advantages of acyclovir. One of these instances had splenomegaly, and three of these cases had significant pulmonary illness. After being hospitalized, one of the three pulmonary cases experienced deteriorating lung involvement, which was treated with remdesivir and dexamethasone. In 29 patients, acyclovir was shown to be affordable, safe, and effective. Treatment is still ongoing for nine people. Thus far, this treatment has not been associated with any side effects or fatalities. To confirm the benefits of acyclovir for SARS-CoV-2 infection, more research comparing acyclovir to remdesivir is required [46].

In a review of Heidary *et al.* Of the 90 publications, 11 reported co-occurring laboratory-confirmed cases of COVID-19 and herpes infection treated with antiviral medication for herpes. In addition to routine COVID-19 management, 28 patients (aged 7 to 82 years) with confirmed laboratory reports of COVID-19 were treated concurrently with antiviral therapy. COVID-19 was detected using an RT-PCR test (reverse transcription polymerase chain reaction), and no mortality was reported. When these 28 patients began treatment, their mean age was 56.4 (range 7–82) years, of which 18 patients were male (64.3%). There was no recorded death from the twenty patients who had acyclovir and the eight who received the other two antiviral medications, valacyclovir in seven cases and famciclovir in one [47].

According to Shors, a 49-year-old woman developed herpes zoster on the 7th day after the start of COVID-19 symptoms. The RT-PCR test confirmed the COVID-19 diagnosis, and the patient started valacyclovir 1 g three times daily. Treatment for the skin lesions was sluggish to take effect, and she experienced severe neuralgia that was only mildly better with topical lidocaine and oral gabapentin [48].

In a separate trial, acyclovir or valacyclovir was administered in addition to standard COVID-19 treatment to 11 of 15 patients with laboratory-confirmed COVID-19 who had reactivated herpes simplex virus (HSV) or herpes zoster virus (HZV) at the same time. 8 patients had suffered from orolabial lesions caused by HSV that recurred, and seven had localized HZV, of which two had ocular HZV. 6 to 32 days passed between the start of COVID-19 symptoms and the appearance of skin sores due to herpes. Three patients had their vesicle fluid tested by RT-PCR, and the results showed no evidence of severe coronavirus 2. There were no deaths or cases with a poor prognosis reported in this article [49].

Four cases of COVID-19 with laboratory confirmation and varicella zoster virus reactivation were treated with standard COVID-19 therapy and acyclovir. Post-herpetic neuritis was avoided in all instances that were treated. Necrotic herpes zoster lesions involving the second branch of the trigeminal nerve were observed in three cases. There were characteristic herpes zoster lesions in the fourth instance reported by Tartari *et al.*[50].

11. Conclusions

Treatment of COVID-19 infections remains a complex and evolving challenge. Continued research, collaboration among healthcare professionals, and adherence to public health guidelines are crucial for mitigating the virus's impact and developing effective therapeutic interventions. This review has discussed the epidemiology of viral infections, pathogenesis, prevalence and diagnosis of respiratory viruses, symptoms of disease, structure and epidemic potential of coronavirus, pathological effects of SARS-COV2 infection on alveolar epithelial cells, available treatment for the disease, the role of acyclovir in COVID-19, clinical trials in COVID-19 and some reported case studies of the use of acyclovir in COVID-19 infections. Acyclovir is a safe, effective, and affordable drug that reduces the immediate and potential long-term effects of SARS-CoV-2 infection in humans. It has also shown promise in avoiding hospitalization for high-risk persons suffering from mild to critical disease.

Author Contributions

Conceptualization, V.G. and S.P.; methodology, S.P.; software, S.P.; validation, V.G., M.V., and A.V.; formal analysis, V.G.; investigation, S.P.; resources, S.P.; data curation, V.G.; writing—original draft preparation, S.P.; writing—review and editing, V.G. and M.V.; visualization, A.V.; supervision, V.G. and M.V.; project administration, V.G.; funding acquisition, A.V. All authors have read and agreed to the published version of the manuscript.

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Data Availability Statement

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Conflicts of Interest

The authors declare no conflict of interest.

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