

Respiratory RNA Viruses: How to Be Prepared for an Encounter with New Pandemic Virus Strains

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Abstract—The characteristics of the biology of influenza viruses and coronavirus that determine the implementation of the infectious process are presented. With provision for pathogenesis of infection possible effects of serine proteinase inhibitors, heparin, and inhibitors of heparan sulfate receptors in the prevention of cell contamination by viruses are examined. It has been determined that chelators of metals of variable valency and antioxidants should be used for the reduction of replicative activity of viruses and anti-inflammatory therapy. The possibility of a pH-dependent impairment of glycosylation of cellular and viral proteins was traced for chloroquine and its derivatives. The use of low-toxicity drugs as part of adjunct therapy increases the effectiveness of synthetic antiviral drugs and interferons and ensures the safety of baseline therapy.

Keywords: RNA viruses, chloroquine, inhibitors of serine proteinases, cell contamination prevention

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INTRODUCTION

Humanity is faced with the emergence of new, previously unknown strains of virulent respiratory viruses that threaten the death of a large number of people with mystical regularity. Influenza viruses and coronaviruses, which have been in contact with people since ancient times, pose a particular epidemic/pandemic danger.

It is believed that the first major outbreak of respiratory infection clinically similar to influenza was described in detail by Hippocrates as early as 412 BC as a contagious “Perinthian cough” (Kuszewski and Brydak, 2000; Pappas, 2008). The next detailed write-up of influenza-like epidemic respiratory disease known as the “peasant fever” of 1173–1174 was only compiled 1500 years later in England (Potter, 2001). The first influenza pandemic is well-defined in 1580 (Potter, 2001; Daly et al., 2007). At the same time, in the 16th century, this infectious disaster was called “influenza” (influence, from Latin), since this disease at that time was considered a bad “influence of heaven” (Broxmeyer, 2006). Since then, 31 influenza pandemics have been recorded, three of which were observed in the 20th century and one took place in the 21st century (Kilbourne, 2006; Daly et al., 2007; Al-Muharrmi, 2010) (Table 1).

Although a targeted search for pathogens capable of causing epidemics/pandemics of acute respiratory infections began at the end of the 19th century (Pfeiffer, 1893; Olitsky and Gates, 1921a, 1921b), the type-A influenza virus *Mixovirus influenza* was isolated only in 1933 (Smith et al., 1933). B- and C-types of influenza viruses were identified in 1940 and 1947, respectively (Francis, 1940; Taylor, 1949), and only in 2011 the type-D influenza virus was isolated and characterized (Hause et al., 2013; Ducatez et al., 2015).

Coronaviruses are also characterized by blanket distribution (Suzuki et al., 2005; Koetz et al., 2006; Sloots et al., 2006; Zhao et al., 2008) and seem to have been in contact with humans since ancient times (Wertheim et al., 2013). Until recently, it was believed that coronavirus infections, which are manifested only by symptoms of an ordinary cold, caused 15 to 35% of seasonal acute respiratory infections. Children get sick five to seven times more often than adults (McIntosh et al., 1970; Callow et al., 1990; Holmes, 2001). In humans, acute respiratory infections are caused by two types of α -coronaviruses (229E and NL63) and two types of β -coronaviruses (OC43 and HKU1) (Gaunt et al., 2010). However, veterinarians have long known that coronaviruses can cause fatal respiratory and intestinal infections in animals (Pensaert, 1999). As a

Table 1. Influenza pandemics of the last century

Pandemic (name)	Years	Strain	Number of deaths (million people)
Spanish flu	1918–1920	H1N1	40–50
Asian flu	1957–1958	H2N2	1–2
Hong Kong flu	1968–1970	H3N2	0.5–2
Swine flu	2009–2010	H1N1	0.5

potential biological threat, coronaviruses have posed a real challenge to modern medicine. In recent decades, new pandemic strains of coronaviruses that are extremely dangerous to humans have often emerged: severe acute respiratory syndrome coronavirus (SARS-CoV, 2002/2003), Middle East respiratory syndrome coronavirus (MERS-CoV, 2012), and the novel type of pneumonia coronavirus (COVID-19, 2019/2020); they are capable of causing severe, often unfavorable, bronchiolitis and pneumonias (Cherry, 2004; Ramadan and Shaib, 2019; Hui et al., 2020).

Human coronaviruses were first isolated from patients with acute respiratory diseases in 1965 (Hamre and Procknow, 1966; Tyrrell and Bynoe, 1966). Electron microscopy showed them to have a coronal structure feature, what is subsequently reflected in their name (Tyrrell et al., 1975). Since then coronaviruses attracted little attention from researchers for nearly three decades (before the emergence of pandemic strains).

It is clear that pandemics of respiratory viral infections have plagued humankind in the past, and there is no reason to believe that this will not happen in the future. The time and place of the emergence of new pandemics and virulence of pandemic virus strains cannot be predicted.

BIOLOGICAL CHARACTERISTICS OF INFLUENZA VIRUSES AND CORONAVIRUSES

Influenza viruses belong to the family of orthomyxoviruses (Orhtomyxoviridae, RNA viruses with a segmented genome) and are divided into four monotypic genera: influenza-A viruses (*Alphainfluenza virus*), influenza-B viruses (*Betainfluenza virus*), influenza-C viruses (*Gammainfluenza virus*), and influenza-D viruses (*Deltainfluenza virus*), each of them is represented by only one type of virus of the same name. It is believed that only influenza-A viruses have pandemic potential (Bouvier and Palese, 2008; Spickler, 2016; King et al., 2018). Influenza-A viruses are subdivided into subtypes with respect to the antigenic properties of hemagglutinin HA (the glycoprotein of the virion envelope, which ensures the recognition of target cells and the binding of viral particles to terminal residues of sialic acids of the glycoproteins of the plasma membrane of epithelial cells) and neur-

aminidase NA (exo- α -sialidase, which catalyzes the cleavage of the glycosidic bonds of the terminal residues of sialic acids of oligosaccharides, glycoproteins, glycolipids and thereby allows the release of daughter influenza virions from infected cells).

In total, there are 18 known serotypes of hemagglutinin (H1–H18) and 11 identified serotypes of neuraminidase (N1–N11); therefore, it is theoretically possible to form 198 different combinations of these proteins, subtypes of the influenza-A virus (Skehel, 2009; Tong et al., 2013; Quan et al., 2016; Kosik and Yewdell, 2019; Zhao et al., 2019), of which more than 120 combinations have been identified in nature (Tsai and Chen, 2011; Rejmanek et al., 2015).

Eight negatively polar segments of the RNA genome of the influenza virus encode at least ten structural and nine regulatory proteins (Varga et al., 2011; Muramoto et al., 2013; Hutchinson et al., 2014; Vasin et al., 2014). There is some uncertainty about the proteome of influenza-A viruses due to the fact that, unlike most RNA viruses, the transcription and translation of their genome occurs in the nucleus, not in the cytoplasm of infected cells. This allows influenza-A viruses (Fig. 1) to exploit cellular splicing machinery to generate splice variants of viral mRNAs. In addition, influenza-A viruses seem to use alternative open reading frames to expand their proteome.

Most viral proteins are localized within the viral lipid envelope; only HA and NA, in a molar ratio of about 10 : 1 (Mitnaul et al., 2000), and the M2 protein embedded in the virion envelope carry antigenic determinants available for the action of immune antibodies (Kosik and Yewdell, 2019). HA and NA molecules are extensively glycosylated proteins, which ensures their functional activity and aberration from protective immune responses via screening of antigenic determinants (Kim et al., 2018; York et al., 2019).

Unlike influenza viruses, coronaviruses are enveloped RNA viruses (with nonsegmented, positive-polar RNA) of Nidovirales order, Coronaviridae family, Orthocoronavirinae subfamily (Fehr and Perlman, 2015). Coronaviral virions have spherical shape with characteristic clavate projections (Neuman et al., 2006; Barcena et al., 2009) (Fig. 2). The virion envelope is formed by a lipid bilayer where S-, M-, and E-proteins are fixed (Lai and Cavanagh, 1997; De Haan and Rottier, 2005).

Spike proteins (SPs) function as abundantly glycosylated trimeric complexes (Zheng et al., 2017; Parsons et al., 2019), ensure the interaction of the virion with epithelial cell receptors and the subsequent internalization of the viral genome (Li, 2016).

Membrane proteins (MPs) function as a dimer with a glycosylated N-terminal ectodomain (Nal et al., 2005) and can accept two different conformational states. The conformers of this glycoprotein determine the assembly and shape of the viral particle (Neuman et al., 2011).

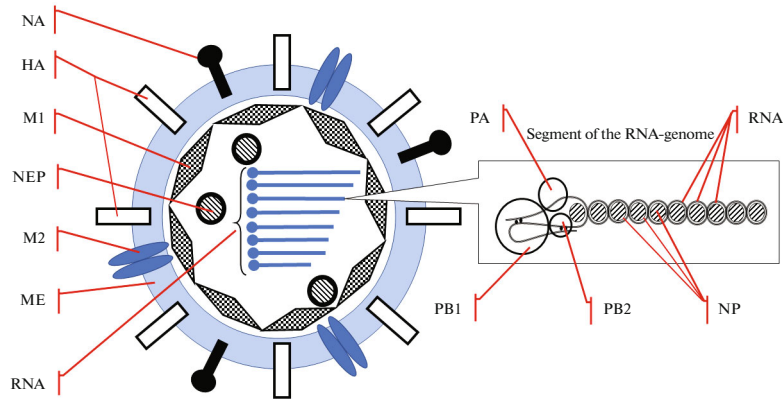


Fig. 1. Structural elements of the type A influenza virus. HA—hemagglutinin (trimer), NA—neuraminidase (tetramer), M1—matrix protein 1, M2—matrix protein 2, ME—phospholipid membrane, NEP—nuclear exporter protein, RNA—negative-strand RNA in ribonucleoprotein segments, NP—nucleocapsid protein, PA—acidic polymerase protein, PB1—basic polymerase protein 1, PB2—basic polymerase protein 2.

Envelope proteins (EPs) are transmembrane proteins that are found in small quantities and perform several functions: virion assembly, envelope formation, and the release of a viral particle from the cell. There are indirect indications that they are glycoproteins (Schoeman and Fielding, 2019).

Nucleoproteins (NPs) are the only proteins found inside the virion. They enable the packaging of the viral genome (McBride et al., 2014).

It is noteworthy that, as in the case of influenza-A viruses, the envelope proteins of coronaviruses are glycoproteins.

The process of cell penetration by the influenza virus consists of several stages. A critical moment in the life cycle of the influenza virus is the recognition of specific cellular receptors, glycoproteins or glycolipids. The glycan contains the terminal α 2,6- or α 2,3-sialic acid (Leung et al., 2012; Byrd-Leotis et al., 2017). The attachment of the HA virion to sialylated glycoproteins and glycolipids of the plasma membrane of epithelial cells initiates various endocytosis mechanisms. This rapidly leads to the formation of endosomes, where each of them contains a viral particle (Chardonnet and Dales, 1970; Matlin et al., 1981; Kartenbeck et al., 1989; Rojek et al., 2008; Nanbo et al., 2010; Watanabe et al., 2010; Boulant et al., 2015).

The next stage of internalization, the release of the viral genome (RNA segments) into the cell cytosol, depends on the activity of Na^+/K^+ -ATPase, which is localized in the endosomal membrane and functions as a proton pump.

The Na^+/K^+ -ATPase results in acidification of the medium inside endosomes/lysosomes to a pH of 5.0 (Cain et al., 1989). Acidification of the intraendosomal medium, i.e., the accumulation of H^+ protons in the endosome content, makes it possible to realize the protonophore potential of the tetramers of the M2

protein of the viral-particle envelope (Sugrue and Hay, 1991; Pinto et al., 1992; Manzoor et al., 2017). The penetration of hydrogen ions into the viral particle mediates conformational changes and decomposition of the structural components of the virion envelope and, ultimately, leads to labilization of its genome (Shibata et al., 1983; Yoshimura and Ohnishi, 1984). However, the fusion of the envelope of the viral particle and the endosomal membrane, which ensures the release of the RNA genome of the virus into the cell cytosol, is possible only with the participation of the HA virion, which undergoes preliminary proteolytic processing by serine (secretory trypsin-like) proteinases (Klenk, 1975; Lazarowitz and Chopin, 1975; Tashiro et al., 1987; Steinhauer, 1999; Kido et al., 2009).

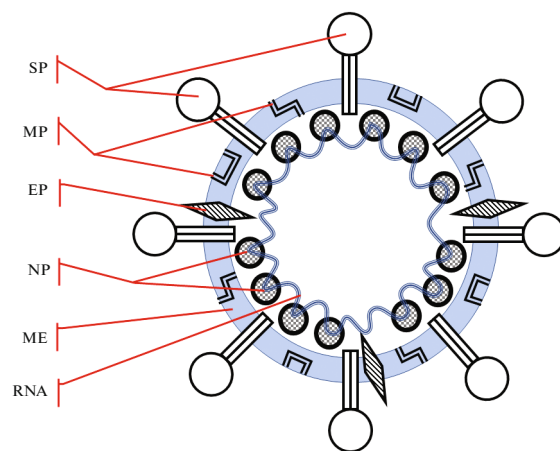


Fig. 2. Structural elements of the coronavirus virion. SP—S-protein (trimer), MP—dimer of the membrane protein in various conformations, EP—transmembrane envelope protein, ME—phospholipid membrane, RNA—positive-strand RNA, NP—nucleocapsid protein.

Translocation of RNA segments of the influenza-virus genome from the cytosol into the cell nucleus is necessary for their replication. During this process viral mRNAs of the nucleus enter the cytosol for consequent synthesis of proteins of viral particles. Self-assembly of virions occurs on the apical part of the plasma membrane of epithelial cells, where HA and NA molecules are concentrated (Samji, 2009; Dou et al., 2018).

The internalization process of coronaviruses is determined by functional activity of the virion SP envelope. The coronaviral SP is strongly glycosylated structure that enables the fixation of viral particles on the plasma membrane of epithelial cells and the subsequent release of their RNA genome into the cell cytosol (Li, 2016; Watanabe et al., 2020). Each SP has two receptor-binding domains localized on its S1 subunit; they are capable of interacting either with specific proteins or with sialoglycans of epithelial cells (Li, 2012; Shahwan et al., 2013; Hulswit et al., 2019). For example, MERS-CoV preferentially binds to α 2,3-linked sialic acid (to a lesser extent to α 2,6-linked sialic acid) (Li et al., 2017). The COVID-19 viruses appear to have a similar affinity for α 2,3-sialic acid conjugates.

Internalization of the viral genome can occur either through endocytosis of the virion (the process is largely similar to the process of internalization of influenza viruses) or by fusion of the coronavirus envelope and the plasma membrane of the epithelial cell without endosome formation (directly on the plasma membrane). In any case, the release of the RNA genome of the virus into the cytosol of the cell is preceded by proteolytic cleavage of the S1 subunit and modulation of the S2 subunit of SP by serine proteases (Bosch et al., 2003; Belouzard et al., 2009; Simmons et al., 2013; Heurich et al., 2014; Zumla et al., 2016).

In the cytoplasm of the epithelial cell, the RNA genome of the virus functions as mRNA, when the replication-transcriptional complex also enables replication of the RNA genome and the mRNA synthesis of structural proteins of the viral particle (Sola et al., 2015; Nakagawa et al., 2016). Following posttranslational glycosylation in the Golgi apparatus cisterns newly synthesized coronavirus proteins (Nal et al., 2005; Tseng et al., 2010) enter the cytosol and provide self-assembly of viral particles, which subsequently migrate to the cell membrane as part of the vesicles and leave the cell through exocytosis (Fehr and Perlman, 2015; Lim et al., 2016).

Due to the importance of serine proteinases, glycoproteins, and glycolipids in the life cycle of influenza viruses and coronaviruses, it can be assumed that factors modulating the glycosylation profile of proteins and lipids of epithelial cells and viruses and controlling the activity of serine proteinases on the epithelial lining of the respiratory tract can significantly limit the virulence of influenza viruses and coronaviruses.

GENETIC EVOLUTION OF INFLUENZA-A VIRUSES AND CORONAVIRUSES

Influenza viruses, when circulating in natural reservoirs, are characterized by high genetic variability, which is manifested in the formation of quasi-subtypes (immunologically distinct antigenic variants) of A viruses (Barbezange et al., 2018). This biological feature, antigenic drift (Taubenberger and Kash, 2010), is stipulated by the fact that the RNA-dependent RNA polymerase of influenza viruses does not have an active correction site (Steinhauer et al., 1989; Cheung et al., 2014). This leads to a high frequency of point mutations in the course of RNA genome replication (300 times more often than during the replication of the bacterial DNA genome) (Drake, 1993). Their other distinguishing characteristic is a high mutational tolerance of the envelope glycoproteins of viral particles, i.e., the ability of HA and NA to maintain functional activity with significant changes in a primary structure of the polypeptide chain (Thyagarajan and Bloom, 2014; Visher et al., 2016).

An important and widespread phenomenon in the evolution of influenza-A viruses is antigenic shift (Holmes, 2005; Dugan et al., 2008). Antigenic shift is the exchange of RNA segments of the viral genome encoding the structure of HA and/or NA in cases of simultaneous infection of the cell with several strains of the influenza-A virus (Taubenberger and Kash, 2010). It is antigenic shift that allows new subtypes of the type-A influenza virus to overcome interspecies barriers (Scholtissek et al., 1978; Garten et al., 2009).

Unlike other RNA viruses, RNA-dependent RNA polymerase, which has 3'-exonuclease correcting activity, is involved in the replication of the coronavirus genome (Smith et al., 2014). In order to evade the mechanisms of the immunoresponse of the human body and to preserve the genotype in the *Homo sapiens* population, as shown by the example of the HCoV-OC43 strain, coronaviruses also maintain a state of antigenic drift (Ren et al., 2015). In addition, the coronaviral genome also evolves through RNA-RNA recombinations (Keck et al., 1988; Huang et al., 2016; Forni et al., 2017). Homologous RNA recombination is the redistribution of genetic material by means of the exchange of regions of the RNA genome of viruses under conditions of coinfection (Makino et al., 1986; Lai, 1990; Lai and Cavanagh, 1997). In addition to aberration of the host immunoresponse mechanisms, RNA recombination allows coronaviruses to change the virulence profile and tissue tropism and to overcome interspecific barriers (Haijema et al., 2003; Stavrinides and Guttman, 2004).

A high genetic and phenotypic variability of influenza-A viruses and coronaviruses is fraught with the acquisition of resistance by these pathogens to specific medical and prophylactic agents, as well as the sudden appearance of new virulent pandemic strains.

PANDEMIC OF RESPIRATORY VIRAL INFECTIONS AND THE PROBLEM OF PNEUMONIA

The influenza pandemic of 1918–1920, the most fatal event in the history of mankind, carried away lives of more than 50 million people (Johnson and Mueller, 2002). Mortality during pandemics of influenza and coronaviruses is, to a large extent, associated with pneumonia (Morens et al., 2008; Metersky et al., 2012; Yin and Wunderink, 2018; Al-Baadani et al., 2019). Primary viral pneumonias are often complicated by bacterial coinfection, i.e., they turn into viral-bacterial and bacterial pneumonias (Oswald et al., 1958; Bisno et al., 1971; Palacios et al., 2009; Gill et al., 2010; Martin-Loeches et al., 2011; Cilloniz et al., 2012). Therefore, there is a widespread opinion among infectious disease specialists that was formulated by Louis Cruveilhier in 1919: “Si la grippe condamne, la surinfection exécute, a-ton dit avec raison” (Cruveilhier, 1919, 448 p.).

At the same time, the clinical picture of severe viral respiratory infections is often represented by a symptom complex of primary viral pneumonia. The emergence of primary viral pneumonia during respiratory viral infections is apparently associated with the copresentation of glycoproteins and glycolipids. They differ in the presence of glycans with terminal α 2,3-linked sialic acid (which acts as a receptor for respiratory viruses), with the transmembrane serine proteinase TMPRSS2 (which proteolytically activates HA and SP of virions) on the plasma membranes of epithelial cells of alveoli and bronchioles (Ibricevic et al., 2006; Shinya et al., 2006; Kumlin et al., 2008; Bertram et al., 2010; Limburg et al., 2019; Tortorici et al., 2019).

The formation of a susceptibility to bacterial coinfection during respiratory viral pandemics is associated with many factors, such as

- a virus-induced dysbiotic state and impaired barrier function of the epithelial lining of the respiratory tract (Pittet et al., 2010; Ellis et al., 2015; Nita-Lazar et al., 2015; Hanada et al., 2018; Sencio et al., 2020);

- virus-induced dysfunction of the effector cells of the immune system (McNamee and Harmsen, 2006; Small et al., 2010; Ghoneim et al., 2013; Sun and Metzger, 2014) and the immunosuppressive activity of cytokines in relation to antibacterial immunity (van der Sluijs et al., 2004; Cao et al., 2014; Shepardson et al., 2019);

- virus-associated dysfunction of the alveolar-capillary barrier (McAuley et al., 2007; Henkel et al., 2010; Short et al., 2016; Kamal et al., 2017) and suppression of the activity of ion pumps that ensure the absorption of fluid from the lumen of the alveoli (Carlson et al., 2010; Peteranderl et al., 2016; Brand et al., 2018).

Pneumonia associated with respiratory viral infections is an independent factor in the severity of disease and mortality (Maruyama et al., 2016; Ishiguro et al., 2017). So, to a large extent, the main problem of severe viral infections, both in the past and the present, is a problem of viral, viral-bacterial, and secondary bacterial pneumonias.

BASIS FOR DIRECTIONS OF PATHOGENETIC THERAPY

The biology of influenza viruses and coronaviruses inevitably leads to the emergence of new pandemic strains, and their time of occurrence, genetic characteristics and antigenic properties cannot be predicted. That is, pandemics of new respiratory infections will always begin in the absence of specific immune prophylaxis and therapy for these infections. The latter predetermines the need for an early search and development of pathogenetic agents and methods for the prevention/therapy of respiratory viral infections in terms of biology of coronaviruses and influenza-A viruses.

The nature of RNA viruses suggests the effectiveness of systemic administration of interferon preparations (viferon, intron A, reaferon, etc.) for baseline nonspecific therapy for the infections caused by them, with allowance for the asthenization caused by medicines. The effectiveness of topical administration of interferon solutions is doubtful and can be considered in the presence of local symptoms (rhinitis, pharyngitis, etc.). The use of interferon inducers (amixin, cycloferon, neovir, etc.) involves the formation of secondary immunosuppression in 10–14 days, which can lead to reinfection in the ongoing epidemic period. The drugs of basic antiviral therapy also include targeted agents that affect the replication of the viral genome: oseltamivir, triazavirin, and ribavirin, which is the strongest but also the most toxic of the drugs in this group. There are also targeted antiviral agents (lopinavir, ritonavir, nelfinavir) (Yamamoto et al., 2020). Antireplicative activity was traced for the purine derivative, isoprinosine, which is active against influenza-A and -B viruses.

Up-to-date knowledge about the nature of viruses and the formation of the infectious process makes it possible to consider the possibility of widespread use of pathogenetic therapy, the effectiveness of which has been traced in various studies.

It is known that serine proteinases are involved in the provision of internalization of coronaviruses and influenza-A viruses into epithelial cells (Simmons et al., 2013; Garten et al., 2015). The activity of trypsin-like proteinases tract largely depends on the activity of secretory inhibitors of leukoproteinases in the upper respiratory and on the surfactant in the lower regions (Kido et al., 2004). Thus, drugs that have the ability to induce the expression of inhibitors of secre-

tory leukoproteinases and surfactant and their direct inhibitors can significantly inhibit the multicyclic replication of RNA viruses.

Quercetin has all these properties. In addition to its antioxidant effects, e.g., chelation of metals of variable valence (Gholampour and Saki, 2019), stimulation of the expression of antioxidant enzymes (Chen et al., 2017), a direct reduction of free radicals of fatty acid residues of phospholipids and oxidized forms of vitamin E (Chepur and et al., 2020; Ozgen et al., 2016), quercetin in the micromolar concentration range inhibits the activity of serine proteinases (Xue et al., 2017; Jo et al., 2019) and shields the active center of HA of the influenza-A virus (Wu et al., 2015), which gives it a wide range of antiviral effects (Zakaryan et al., 2017).

Trans-4-[[[(2-amino-3,5-dibromophenyl)methyl]-amino]cyclohexanol hydrochloride (as ambroxol or lazolvan) is also gaining attention as an antiviral adjunct (Yang et al., 2002; Yamaya et al., 2014). The spectrum of pharmacological activity of ambroxol, in addition to its mucolytic effect (Rogers, 2007), includes

- antibacterial and antibiofilm effects (Lu et al., 2010; Li et al., 2011; Cabral-Romero et al., 2013; Cataldi et al., 2014);

- the ability to exhibit the activity of a chemical chaperone (Bendikov-Bar et al., 2013; Sanchez-Martinez et al., 2016), a modulator of surfactant secretion (Yang et al., 2002; Seifart et al., 2005), and to provide anti-inflammatory (Gibbs et al., al., 1999; Beeh et al., 2008; Gupta, 2010) and antioxidant action (Nowak et al., 1994; Štětinová et al., 2004);

- the ability to (respiratory organs) stimulate locally the secretion of immunoglobulins IgA and IgG (Yang et al., 2002) and to provide a local anesthetic effect (Kern and Weiser, 2015).

Ambroxol, which possesses the listed properties and is characterized by high bioavailability when administered perorally (Jauch et al., 1978), can be included in the list of drugs used to treat viral pneumonia.

Virus-induced oxidative stress plays a significant role in the pathogenesis of respiratory infections (Schwarz, 1996; Lin et al., 2006; Liu et al., 2017; Khomich et al., 2018). Xanthine oxidoreductase (XOR) plays a leading role in the formation of a symptom complex of manifestations and complications of virus-associated pneumonia. XOR is a cytosolic enzyme of purine catabolism (Frederiks and Vreeling-Sindelárová, 2002; Agarwal et al., 2011). Its activity rapidly increases under hypoxic conditions (Poss et al., 1996; Terada et al., 1997; Linder et al., 2003) and under the influence of pro-inflammatory mediators and cytokines (Page et al., 1998; Brandes et al., 1999). Under pathological conditions, XOR is released from cells into blood (the oxidase form of the enzyme predominates) (Spiekermann et al., 2003) and is fixed on the luminal surface of the plasma membrane of endo-

theliocytes in the inflammation zone through physicochemical interaction with glycosaminoglycans (Rouquette et al., 1988; Akaike et al., 1990; Adachi et al., 1993). XOR, which is localized on the cytoplasmic membrane of endothelial cells, produces a superoxide radical anion during purine oxidation and can simultaneously reduce nitrite and nitrate anions to nitric oxide NO^{\bullet} at another active site (Jansson et al., 2008; Cantu-Medellin and Kelley, 2013), i.e., it can recycle this vasodilating agent. The local production of the complex of prooxidants $\text{O}_2^{\bullet-}$, H_2O_2 , NO^{\bullet} and ONOO^- is potentially very dangerous, especially in the vascular bed of lungs. However, attempts to use the XOR inhibitor allopurinol (Pacher et al., 2006; George and Struthers, 2009) as a therapeutic agent for pneumonia induced by type-A influenza virus in the range of daily doses of 5–50 mg/kg were unsuccessful. Allopurinol had no effect on the course and the outcomes of viral infection (Dolganova and Sharonov, 1997), because the NADH oxidase and nitrite/nitrate reductase activities of XOR, which are realized by the FAD-dependent enzyme site, is not affected when the molybdopterin-containing center of the enzyme is inhibited by allopurinol (Harris and Massey, 1997; Doel et al., 2001; Boueiz et al., 2008). Since there are still no drugs that can inhibit the FAD-dependent activity of XOR, the prescription of heparin, which releases XOP from the connection with glycans and promotes its elimination from the focus of inflammation, is advised in order to prevent pulmonary thromboembolism and to desorb the enzyme from the cytoplasmic membrane of endothelial cells heparin (Povalyaev, 2014; Obi et al., 2019).

Mitochondria are another significant source of reactive oxygen species and metabolites in respiratory viral infections (To et al., 2020). Melatonin as a mitochondrial antioxidant (Reiter et al., 2017) that exhibits anti-inflammatory and immunomodulatory effects, has a pronounced beneficial effect on the course and outcomes of viral infections in the experiment (Srinivasan et al., 2012; Silvestri and Rossi, 2013; Tan et al., 2014; Huang et al., 2019; Zhang et al., 2020).

The superoxide radical anion with respect to organic and inorganic chemical compounds, depending on their chemical nature, can play the role of both an oxidizing agent ($E_0 \text{O}_2^{\bullet-}/\text{H}_2\text{O}_2 = +0.89 \text{ V}$) and a reducing agent ($E_0 \text{O}_2/\text{O}_2^{\bullet-} = -0.16 \text{ V}$) (Wood, 1987, 1988). The reductive properties of the superoxide radical produced in pessimal amounts during viral pneumonia in the inflammation zone determine the possibility, in particular, of the reduction of iron ions and their release from complexes with biomacromolecules. For example, in the ferritin composition, iron is presented in the form of Fe^{3+} ions, which, under the influence of the superoxide radical anion, become Fe^{2+} and leave the above protein (Biamond et al., 1984; Bolann and Ulvik, 1987). In the presence of free

iron ions and partially reduced oxygen species, conditions arise for the functioning of a kind of catalytic reactor for the redox catabolic production of prooxidants and, in particular, an extremely toxic hydroxyl radical (Morris et al., 1995). This is also an extremely dangerous state of the biological system, because biological fluids in the presence of free iron ions lose their antibacterial properties (Bullen et al., 1991; Griffiths, 1991; Sritharan, 2006).

The removal of free iron ions from biological media of the organism is a matter of life and death in the course of viral pneumonia. However, attempts to use available chelators (deferoxamine) to bind iron ions in viral pneumonia not only did not have a positive effect on the course of the pathological process, but, contrary to expectations, increased mortality (Dolganova and Sharanov, 1997). The explanation for this paradox is that deferoxamine (desferal), which has an affinity constant for iron ions approximately equal to the siderophores of microorganisms (Hallaway et al., 1989; Askwith et al., 1996), is not able to limit the availability of Fe^{3+} for pathogenic microorganisms (Kim et al., 2007; Cassat and Skaar, 2013). At the same time, iron ions chelated with deferoxamine apparently do not completely lose the ability to undergo redox transformations and, thus, secure the course of the Fenton and Osipov reactions (Borg and Schaich, 1986; Klebanoff et al., 1989; Dulchavsky et al., 1996; Niihara et al., 2002; Francisco et al., 2010).

In contrast, 2-ethyl-6-methyl-3-hydroxypyridine succinate (mexidol, emoxipine) is characterized by a pronounced iron-chelating effect (Andrusishina et al., 2015), antioxidant activity (Voronina, 2001), and the properties of an inhibitor of serine and matrix proteinases (Zolotov et al., 1989; Akhmedov et al., 2009). With such a list of biological effects, Mexidol can be effectively used as an adjunct in the treatment of pneumonia (Ilyashenko et al., 2003; Luzhnikov et al., 2006) and viral infections (Laseeva, 2009; Pavelkina, 2010).

Chloroquine (in the form of phosphate, hydrochloride or sulfate) has been widely used in clinical practice for more than seven decades, since 1947 (Solomon and Lee, 2009), as a safe, effective and affordable drug:

- for the prevention and treatment of malaria (Mengesha and Makonnen, 1999; Bello et al., 2010; Waqar et al., 2016);

- in the treatment of leprosy (Meinao et al., 1996; Bezerra et al., 2005; Gordon et al., 2018);

- as an anti-inflammatory agent in the treatment of rheumatoid arthritis (Augustijns et al., 1992; Schrezenmeier and Dorner, 2020);

- in a treatment for antiphospholipid syndrome (Tektonidou et al., 2019);

- in the treatment of Sjogren's syndrome (Vivino et al., 2016; Shivakumar et al., 2018; Lee et al., 2019);

- in the treatment of amoebic hepatitis and liver abscesses (Sodeman et al., 1951; Cohen and Reynolds, 1975);

- in the treatment of malignant neoplasms as a means of sensitization (Solomon and Lee, 2009; Maycotte et al., 2012; Kimura et al., 2013);

- in the treatment of metabolic syndrome (Kastan et al., 2007; McGill et al., 2019) and inflammatory diseases of bacterial etiology (as a synergist of antibiotics) (Crowle and May, 1990; Feurle et al., 2012; Son and Chung, 2014).

Chloroquine and its analogs (Delagil, Plaquenil, Immard, Mefloquine, etc.), which exhibit the properties of weakly alkaline amines, easily overcome cell membranes in a nonprotonated form (Chinappi et al., 2010) and, after undergoing protonation, accumulate in closed cell compartments with acidic pH values (endosomes, lysosomes) (Vincent et al., 2005). The chloroquine level in them can be more than two orders of magnitude higher than its concentration outside the cell (De Duve et al., 1974). Without entering into biotransformation reactions, chloroquine can remain in isolated intracellular compartments for hundreds of hours (Schrezenmeier and Dorner, 2020).

Chloroquine accumulates in endosomes/lysosomes, shifts the pH value towards the basic values (Homewood et al., 1972; Ohkuma and Poole, 1978; Al-Bari, 2017), and inhibits various ATPases, including H^+ -ATPase (V-ATPase), which determines the acidification of the of endosomes and cisterns of the Golgi apparatus (Chandra et al., 1992; Bhattacharyya and Sen, 1999; Holliday, 2017). It is possible that the above mentioned phenomena determine the block of release of fragments of the RNA genome of influenza viruses from lipoproteins of their envelope (Shibata et al., 1983), which leads to the suppression of virion replication (Ooi et al., 2006; Di Trani et al., 2007).

The ability of chloroquine to inhibit the acidification of endosomes containing respiratory viruses, and thus block the release of their RNA genomes and subsequent replication are difficult to accept as a satisfactory explanation for its antiviral activity. The fact is that chloroquine exhibits high antiviral activity not only against influenza A viruses (internalization in endosomes) but also against coronaviruses (Keyaerts et al., 2004; Vincent et al., 2005; Ooi et al., 2006; Yan et al., 2013; De Wilde et al., 2014; Kearney, 2020). Their internalization almost exclusively occurs by means of membrane fusion, i.e., without the stage of endosome formation (Matsuyama et al., 2005).

Among the three types of biological aperiodic polymers (nucleic acids, polypeptides, carbohydrates), aperiodic carbohydrate polymers (glycans, oligosaccharides) are distinguished by the highest information capacity due to their structural features. This provides a high specificity of ligand-receptor interactions of oligosaccharide conjugates. However, the structure of glycans is encoded in the eukaryotic

genome not directly but indirectly. Oligosaccharides are synthesized in the cisterns of the Golgi apparatus with the participation of secondary protein matrices that form functional heterogeneous associations (conveyor lines) of glycosyltransferases (Chepur et al., 2019). Naturally, the spatial structure of such matrix protein molecules and, consequently, their affinity for enzymes of glycan synthesis can rapidly and significantly change under the influence of the dynamics of the pH values and the redox potential of the cistern medium of the Golgi apparatus.

Therefore, it is significant that chloroquine is able to change the redox status of the cell (Giovannella et al., 2015) and to decrease the proton concentration (increase the pH value) in the lumen of the cisterns of the Golgi apparatus by suppressing the activity of ATPases, including H⁺-ATPase (Reaves and Banting, 1994; Hassinen et al., 2011). It is considered that the most sensitive to the dynamics of pH value function of the Golgi apparatus is the synthesis of aperiodic oligosaccharides (Kellokumpu, 2019): an increase in pH by 0.2 units in the lumen of cisterns of the Golgi complex is accompanied by a violation of terminal α 2,3-sialylation of both N-linked and O-conjugated glycans (Rivinoja et al., 2006, 2009). Aberrant glycosylation with a decrease in the acidity of the intraluminal medium of the cisterns of the Golgi complex is apparently associated with a pH-induced change in the topology/position of glycosyltransferases in the multienzyme complexes of the synthesis of aperiodic oligosaccharides.

Since all participants in the interaction of human body cells with respiratory RNA viruses (glycoproteins, glycolipids) contain an ample number with glycans with terminal sialic acids, which serve as specific receptors for viral particles, the chloroquine-induced disruption of sialylation/glycosylation processes of cellular and viral participants in this interaction determines the antiviral effect of drugs in this group.

The involvement of glycans in viral adhesion and replication is extremely important. It should be noted that a number of viruses, including coronaviruses (Milewska et al., 2014, 2018; Szczepanski et al., 2019), use a common heparan sulfate-dependent mechanism of attachment to the cell membrane. Derivatives of dyspirotripiperazine that inhibit the replication of viruses of various families that use heparan sulfate to attach and/or penetrate into the host cell have been obtained (Makarov et al., 2016; Novoselova et al., 2019). The class of compounds involved opens up new possibilities for the inhibition of the process of viral transmission, which has been experimentally proven in a model of infection with the herpes simplex virus of the first type.

A technique used for the prevention/therapy of aspiration and ventilator-associated pneumonia can be adapted for the treatment of virus-associated pneumonia. The main point of the technique is to create a hypoosmotic (up to 200–250 mmol/L) medium for

autoblood erythrocytes in a solution of a broad spectrum antibiotic with the addition of dimethyl sulfoxide and heparin. The latter is used to improve the rheological properties of blood, to desorb XOR from the luminal surface of endothelial cells, and to remove it from the inflammatory focus. Implementation of the approach makes it possible to avoid hemolysis and, when injected intravenously, to use autoblood erythrocytes as a depot for the targeted delivery of drugs to the inflammatory focus, in particular, to the pneumonia focus where they are released. Dimethyl sulfoxide in generally used amounts (0.3–0.4 mL) increases the fluidity (reduces microviscosity) and permeability of cell (erythrocyte) membranes and promotes cellular penetration by the antibiotic without any adverse effects on the structure and functional characteristics of the blood corpuscles (Gurtovenko and Anwar, 2007). Moreover, dimethyl sulfoxide inhibits the activation of pro-inflammatory transcription factors NF- κ B, AP-1 and the expression of the adhesion molecules ICAM-1 (Chang et al., 2001), blocks the transcription of interleukin genes IL-1, -6, and -8 and the activation of NLRP3 by inflammas (Ahn et al., 2014; Elisia et al., 2016), and has a pronounced antioxidant activity at extremely low concentrations (Jia et al., 2010; Sanmartin-Suarez et al., 2011).

Up-to-date knowledge of antibiotic properties makes it possible to select drugs with effects that are not associated with bacteriolysis or the release of pathogen-associated molecular patterns (Tauber and Nau, 2008) and those that can be implemented without activation of the effector functions of polymorphonuclear leukocytes (Rahman and Mazumder, 2001), their chemotaxis (Burgaleta et al., 1982), or an increase in the activity of neutrophil NADPH oxidase (Umeki, 1995; Dutta et al., 2009).

CONCLUSIONS

Respiratory RNA viruses are anthrozoönotic infectious pathogens that have natural reservoirs of infection and form a single dynamic gene pool. A single gene pool involves the exchange of genetic material between the genomes of related human and animal RNA viruses. This inevitably leads to the emergence of new, highly virulent strains of pathogens, the time of occurrence and antigenic properties of which cannot be predicted. That is, epidemics of new, respiratory, RNA viral infections will always begin in the absence of drugs for immune prophylaxis and treatment for these infections. The latter predetermines the need for the early search and development of effective means and methods of pathogenetic prevention/therapy for respiratory RNA viral infections.

COMPLIANCE WITH ETHICAL STANDARDS

Conflict of interests. The authors declare that they have no conflicts of interest.

Statement on the welfare of humans or animals. This article does not contain any studies involving animals performed by any of the authors.

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