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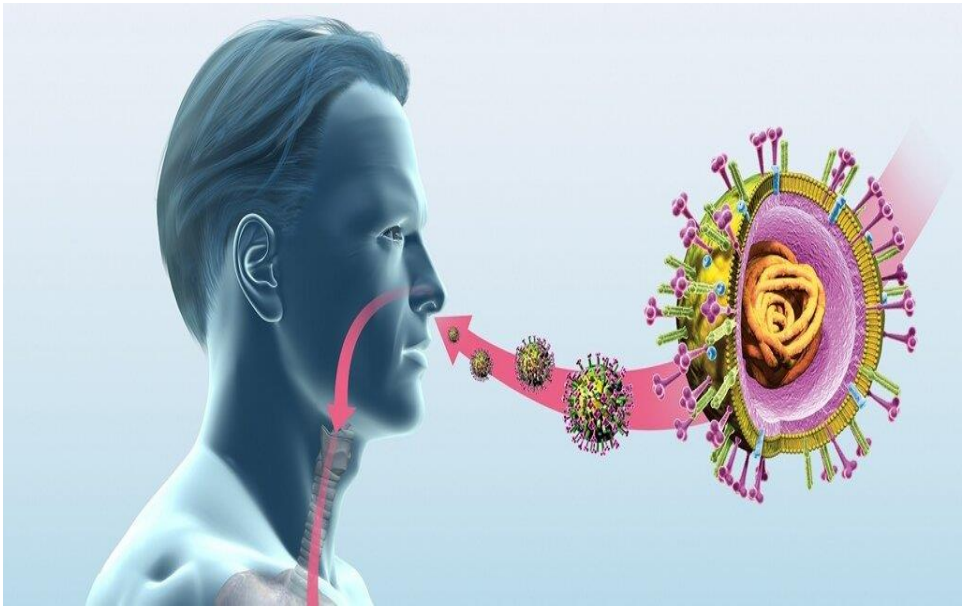
CAUSATIVE AGENTS OF ACUTE RESPIRATORY VIRAL INFECTIOUS DISEASES

(influenza virus, adenovirus, coronavirus)

(I part)

(illustrated textbook)



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The illustrated textbook is intended for students and teachers of medical universities. This illustrated textbook provides a historical background, taxonomy, morphological and tinctorial properties, cultural properties, resistance, epidemiology, epidemiology, pathogenesis, pathogenesis, pathogenesis, virulence factors of the pathogen, clinical presentations, immunity, diagnostics, treatment, prevention of causative agents of acute respiratory viral infections (influenza, adenovirus and coronavirus).

The list of abbreviated words

SARS-severe acute respiratory syndrome
US – United States of America
PHC-primary health care
NR-neutralization reaction
HAI-hemagglutination inhibition reaction
WHO – World Health Organization
DNA-deoxyribonucleic acid
MPI - Medical and preventive institutions
ARI - Acute respiratory viral infections
ELISA- enzyme-linked immunosorbent assay
IFR-immune fluorescence reaction
CBR-complement binding reaction
PCR-polymerase chain reaction
RNA-ribonucleic acid
PHR - indirect (passive) hemagglutination reaction
TEM-transmission electron microscope
IU - international unity

Context

Introduction

The group of acute respiratory (from the Latin respiratio - breathing) viral infections (ARVI) includes a large number of the most common diseases, characterized by the impact of various respiratory and respiratory organs. They often take the first place among all diseases. ARVI can be caused more than 200 viruses that are extremely difficult to diagnose: influenza viruses, parainfluenza, respiratory syncytial virus, rhinoviruses, coronaviruses, reoviruses, adenoviruses, and some seroviruses. All these viruses belong to different families and species, differ between each other in their biological properties and therefore require an individual approach to laboratory research. The following factors contribute to the prevalence of ARVI:

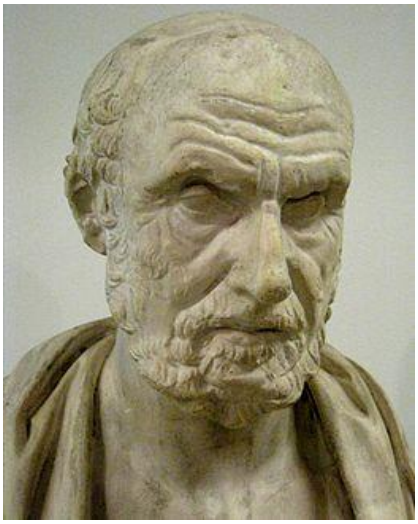
1) a large variety of viruses - the causative agents of ARVI;
2) lack of cross-immunity between them;
3) lack of resistance to recurrent infections;
4) lack of many effective vaccines against them;
5) the most common method of infection (air-droplet way), which causes the rapid spread of the pathogen, which in the absence of immunity can be the cause not only of epidemics, but also pandemics. [1]

Influenza

Influenza (from Old French. Grippe - to grasp, scratch) is an acute infectious viral disease of a person, characterized by damage to the respiratory tract, fever, general intoxication, impaired activity of the cardiovascular and nervous system [2].

Historical background

The first mention of the flu was noted many centuries ago - as early as 412 BC. - it was then that Hippocrates described a disease similar to the flu. Multiple descriptions of influenza epidemics occur in the Middle Ages. Flu-like outbreaks were noted in 1173 [3]. Since the 12th century, humanity has been subjected to more than 130 virological attacks - about the same number of times there have been epidemics and pandemics of influenza [4]. The first documented influenza pandemic that took many lives happened in 1580 [5]. During 1918-1920 there was deadly pandemic - "Spanish flu" caused by the H1N1 virus. The pandemic took, according to various sources, from 20 million to 100 million human lives. The disease affected 20-40% of the world's population. From the "Spanish flu" they died at an incredible speed, in the morning a person could feel good, in the afternoon the first signs of illness appeared, it became sharply worse and by the evening the doctor declared death. Not everyone died instantly, some could survive the first day of the illness, but later death came from pneumonia. The peculiarity of the "Spanish flu", in addition to the increased mortality, was that people under 50 were more susceptible to the disease, although, as a rule, the flu is dangerous for children and the elderly.



Hippocrates (circa 460 BC, island of Kos - circa 370 BC, Larissa) [6]

This was followed by a number of scientific discoveries:

- American Richard Shoupe (pictured), studying influenza in pigs, made a sensational discovery in 1931: an influenza virus was discovered;
- 1933 - influenza type A virus was first identified by virologists Wilson Smith, Christopher Andrews and Patrick Laidlaw (National Institute of Medical Research, London);
1940 - Thomas Francis discovered the type B influenza virus;
- 1940 - it became known that the influenza virus can be cultivated on chicken embryos, which greatly helped science in further research;
- in 1947 - Richard Taylor isolated the type C influenza virus [7].

Richard Shoupe [8]

Wilson Smith [9]

Christopher Andrews [10]

Patients with "Spanish flu" in a hospital in the United States, 1918 [11]

Taxonomy

Influenza viruses belong to the *Orthomyxoviridae* family (Greek *orthos* - correct, straight; *myxa* - mucus) and are RNA-containing complex (enveloped) viruses. They got their name because of the affinity for mucin of the affected tissues and the ability to bind to glycoproteins - the surface receptors of epithelial cells. Orthomyxoviruses have a tropism for the respiratory epithelium.

According to the international taxonomy of viruses, the *Orthomyxoviridae* family includes the genus *Influenzavirus A, the genus Influenzavirus B, the genus Influenzavirus C, the genus Influenzavirus D, the genus Isavirus, the genus Quaranjavirus and the genus Togotovirus*.

Representatives of the genera Influenzavirus cause a disease called influenza. Influenzavirus A, Influenzavirus B, Influenzavirus C viruses cause disease in humans, animals and birds, and Influenzavirus D infects pigs. Representatives of

the genus Isavirus are pathogens for salmon, members of the genus Togotovirus cause disease in vertebrates and invertebrates, and members of the genus Quaranjavirus have been identified in birds and ticks.

Within the genus *Influenzavirus A*, subtypes (subtypes or serotypes) of the virus are distinguished by hemagglutinin and neuraminidase. Within the subtypes there may be serovariants.

The influenza type A virus infects humans and some species of animals and birds, causing epidemics and pandemics with high mortality. By antigenic structure, influenza type A virus is subdivided into subtypes (subtypes, serotypes), and they, in turn, into many variants (serovars).

In the modern nomenclature of human influenza viruses, proposed by WHO in 1980, it is customary to describe the serotype, origin, strain, year of isolation and subtypes of the surface antigens of the influenza virus - neuraminidase (N) and hemagglutinin (H). For example: influenza virus A / Moscow / 10/99 / H3N2. In humans, there are 3 types of hemagglutinin - H1, H2 and H3 and 2 types of neuraminidases N1 and N2 (Fig. 1). To date, 3 subtypes of type A influenza virus are known, caused by the combination of these two surface glycoproteins that have the ability to spread in the human population, causing epidemics and pandemics: H1N1, H2N2, H3N2 [12].

The pronounced instability of the surface antigens of hemagglutinin and neuraminidase leads to high variability of the antigenic structure of the influenza A virus, manifested in the form:

1) antigenic "drift" - a partial renewal of antigenic determinants within one subtype, which leads to the emergence of new strains of the virus and the development of seasonal influenza epidemics. This kind of variability is inherent in influenza viruses type A and B;

2) antigenic "shift", accompanied by a complete replacement of the genome encoding one or both surface antigens. This kind of variability is only seen with influenza type A.

Antigenic "shift" leads to the emergence of new subtypes of hemagglutinin and neuraminidase and, consequently, new subtypes of the type A virus that cause pandemics. [13]

The type B influenza virus usually infects humans and rarely animals. This virus causes sporadic outbreaks in humans, sometimes epidemics.

The type C influenza virus causes sporadic cases of influenza only in humans (more often in children).

Comparative characteristics of influenza viruses are presented in Table 1.

Table 1 - Comparative characteristics of influenza viruses

Criteria	Type A virus	Type B virus	Type C virus
Severity of disease	++++	++	+
Natural reservoir	Present	no	no
Pandemics	Causes	Not cause	Not cause
Epidemics	Causes	Causes	Not causes
Mechanism of antigenic changes	shift, drift	Drift	Drift

[12]

Morphological and tinctorial properties

The influenza virus has a spherical shape with a diameter of 80-120 nm. Filamentous forms are less common. A nucleocapsid of helical symmetry is a ribonucleoprotein (RNP) strand, folded in the form of a double helix, which forms the core of the virion. It is associated with RNA polymerase and endoncleases (P1 and P3). The core is surrounded by a membrane consisting of protein M, which connects the RNP with the double lipid layer of the outer envelope and the spines, consisting of hemagglutinin and neuraminidase. [14]

The main functions of hemagglutinin:

- recognizes a cellular receptor - a mucopeptide with N-acetylneuraminic (sialic) acid;

- ensures the fusion of the virion membrane with the cell membrane and the membranes of its lysosomes, i.e. responsible for the penetration of the virion into the cell;

- determines the pandemicity of the virus (change in hemagglutinin the cause of pandemics, its variability epidemics of influenza);

- has the greatest protective properties, responsible for the formation of immunity.

In influenza A viruses of humans, mammals and birds, 13 types of hemagglutinin differing in antigen were found, which were assigned continuous numbering (from H1 to H13).

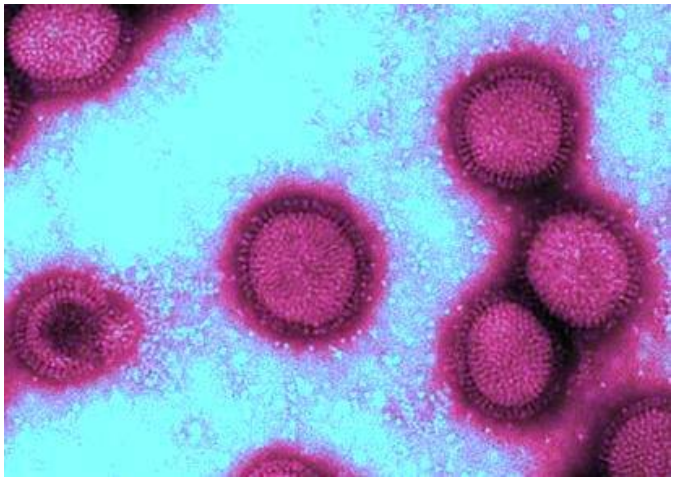
Neuraminidase (N) performs the following functions:

- ensuring the dissemination of virions by cleavage of neuraminic acid from newly synthesized virions and the cell membrane;

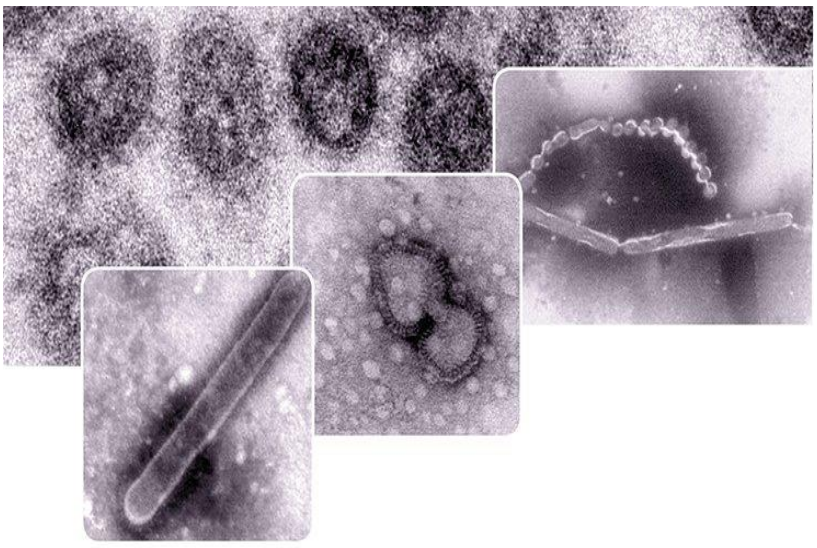
- determination of the pandemic and epidemic properties of the virus together with hemagglutinin.

Influenza A virus has 10 different neuraminidase variants (N1-N10). [15]

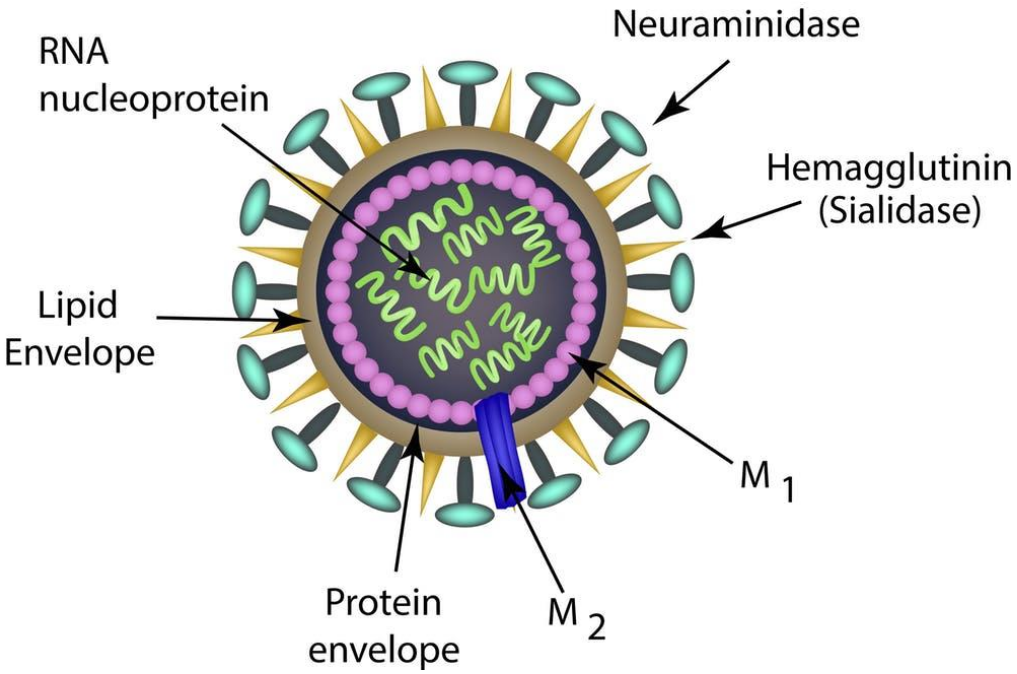
Virions contain about 1% RNA, 70% protein, 24% lipids and 5% carbohydrates. Lipids and carbohydrates are part of the lipoproteins and glycoproteins of the outer shell and are of cellular origin. [14]



Influenza A virus H1N1 [16]



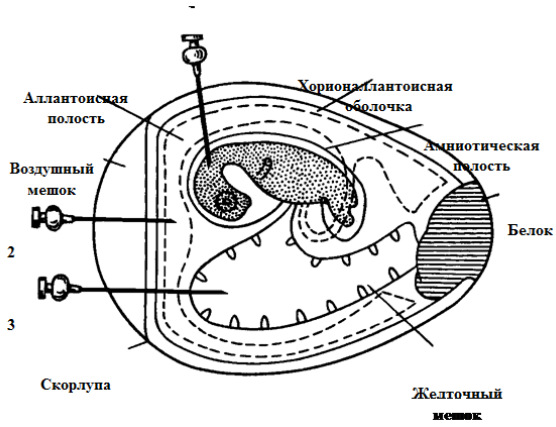
Electron microscopic "portraits" of influenza virus particles (virions) in suspension. Negative contrast can reveal fine details on the surface of viral particles. In the influenza virus, these are, for example, spines, which are molecules of hemagglutinin and neuraminidase [17]



Structure of the virus that cause flu *[18]*

Cultural properties

Influenza viruses are cultured in chicken embryos and in cell cultures. The optimal environment is chicken embryos, in the amniotic and allantoic cavities, of which the virus reproduces within 36-48 hours. The most sensitive to the influenza virus are primary cultures of kidney cells of the embryo of humans and some animals. [14]



Cultivation of influenza virus in chicken embryos [19]

Resistance

The influenza virus is sensitive to heat (at 65^0C it dies within 5-10 minutes), drying, exposure to sunlight, UV light; dies at room temperature in a few hours. It

is easily neutralized by disinfectants, destroyed by ether, which dissolves its lipid membrane, as well as an acidic and alkaline medium. Influenza viruses persist at low temperatures (-70^{0}C). [20]

Epidemiology

Influenza is an anthroponous acute respiratory viral infection with an aerogenic transmission mechanism. [21]

The main mechanism of transmission of influenza viruses is the aerogenic pathway, airborne droplets (when coughing, sneezing, etc.). Contact transmission is also possible (for example, by touching the nasal mucosa with fingers contaminated with the virus). [22]

[23]

Influenza viruses constantly circulate among the population, causing seasonal increases in disease, periodically acquiring the character of epidemics and even pandemics. Influenza epidemics cause huge economic losses and human losses. This primarily applies to type A viruses, which cause epidemics every 2-3 years, and several times a century - pandemics with the spread of infection around the world with the number of cases of 1-2 billion people.Epidemics caused by the type B virus recur after 3-6 years.

Virus C is the causative agent of sporadic diseases, sometimes giving small outbreaks in children's groups.

Influenza pandemics, caused by mutated viruses against which humans have no immunity, occur 2-3 times every 100 years. The 1918-1919 influenza pandemic (Spanish flu, H1N1 strain) killed 40-50 million people. It is believed that the Spanish flu virus arose as a result of the recombination of genes from avian and human

influenza viruses.

-In 1958 pandemic "Asian flu" caused by the H2N2 strain.

-In 1969 the "Hong Kong flu" (H3N2) pandemic. [24]

According to the World Health Organization, from February 2003 to February 2008, out of 361 confirmed human cases of avian influenza A (H5N1) virus, 227 were fatal. The last human death from bird flu was recorded on January 20, 2009 in China.

Since 2009, a new disease in humans and animals has emerged, caused by strains of the influenza virus. Strains associated with outbreaks of the so-called. “Swine flu” are found among influenza viruses of serotype C and serotype A subtypes (A / H1N1, A / H1N2, A / H3N1, A / H3N2 and A / H2N3). These strains are collectively known as swine flu virus. Swine flu is common among domestic pigs, and can also circulate among humans, birds, and other species; this process is accompanied by its mutations.

According to the WHO, as of August 27, 2009, about 255716 cases of infection with influenza A / H1N1 and 2627 deaths were registered in more than 140 regions of the world. In general, the disease with this flu proceeds according to the classical scenario, the frequency of complications and deaths (more often due to pneumonia) does not exceed the average rates for seasonal flu.

The epidemic spread of influenza is facilitated by: intensive reproduction of viruses in the upper respiratory tract and, as a result, a very short incubation period (from several hours to 2 days), massive virus isolation and airborne transmission, (in which one patient can infect a large number of people), high contagiousness of the virus and great susceptibility of people. And, finally, the main feature of the influenza virus, leading to the epidemic spread of the disease, is the ability to antigenic variability - drift and shift, especially pronounced in the type A virus.

Influenza epidemics caused by the type A virus occur in successive pandemic cycles. Each cycle begins with a pandemic, followed by several epidemic waves of influenza, and lasts for 10-30 years. The cycle begins with the emergence as a result of the shift of a new subtype of the A virus with updated surface antigens, capable of causing an influenza pandemic, due to the lack of immunity in the human population to this subtype. With the accumulation of the "immune layer" from the ill people, the morbidity decreases. Under the influence of immunity factors, the selection of point mutants of the initial subtype with minor changes in surface antigens (drift) occurs, and serovariants (strains) appear, causing new waves of influenza epidemic. This

process is repeated - all new antigenic variants of the same pandemic subtype appear, causing subsequent influenza epidemics. The cycle ends after the formation of "herd immunity" to all serovariants of this subtype. It is replaced by the subtype of virus A that has reappeared as a result of antigenic shift, the next pandemic cycle begins; At the same time, the previous subtype disappeared from circulation. An exception was the A / H3N2 / subtype, which has not disappeared from the human population to date, although in 1977 the next pandemic subtype appeared - A / H1N1 / returned after a 20-year absence (Table 1).

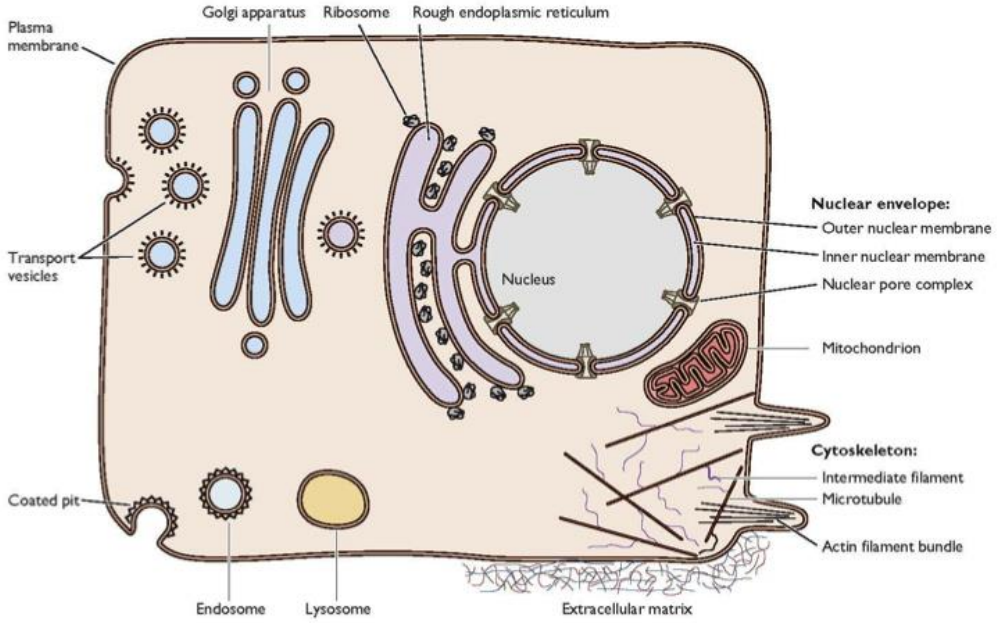
Thus, at present, several serovariants (strains) of both subtypes of virus A, as well as two subtypes of virus B, circulate among the population and cause epidemics. It is possible that a new subtype of virus A may soon appear and the next pandemic cycle will begin. This may be facilitated by the emergence of massive outbreaks of "bird" flu among poultry (chickens, ducks, geese, etc.) in the countries of Southeast Asia, and in 2005 in Russia, Europe and America. It has been revealed that the bird flu virus is carried by migratory birds, mainly waterfowl. The virus is identified as subtype A (H5N1). In Russia, no diseases of "bird" flu in humans have yet been detected, but there have been cases of diseases in Asian countries. There is a danger that recombination between avian and human type A viruses could result in new subtypes of A (shift) virus that could cause an influenza pandemic in humans. [24]

Virulence factors of the pathogen

Almost all genes and virus-specific proteins encoded by them play a key role in the pathogenicity of influenza viruses. These are hemagglutinin, neuraminidase, M2 protein, NS-1, PB1-F2 protein. Hemagglutinin deserves special attention. Changes in its structure form the basis for the evasion of influenza viruses from a specific immune response, and as a receptor-binding protein, it has two key properties: the ability to recognize the cell receptor and determine the ability of the virus to overcome interspecies barriers, and recognition of the neuraminidase receptor determines the ability of the virus to penetrate cells and the development of the reproductive process in them. [25]

The nucleocapsid in influenza viruses is surrounded by a layer of M1 proteins, which make up the inner layer of the lipoprotein envelope. The lipoprotein envelope (supercapsid) is of cellular origin, includes viral transmembrane and bears on the surface spines formed by 2 complex proteins of glycoproteins - hemagglutinin (HA) and neuraminidase (NA). In each virion, the amount of hemagglutinin is many times greater than that of neuraminidase. Type C viruses do not have neuraminidase. On the surface of both glycoproteins, there are special regions for binding to receptors on sensitive cells. For influenza viruses, the

specific receptors are compounds containing sialic acid. Since the composition of sialo-oligosaccharides on cell membranes is different, there is a species and tissue specificity of cell receptors. The interaction of influenza viruses with the cell begins with the fact that hemagglutinins bind to receptors, then neuraminidase cleaves sialic acid from them, and the virus enters the cell by endocytosis. Then the envelope of the virus fusion with the membrane of the endosome and partial deproteinization of the virus. The nucleocapsid enters the cytoplasm, then is transported to the cell nucleus, where gene transcription takes place, in which the proteins of the polymerase complex are involved. The assembly of the nucleocapsid is carried out in the nucleus, where the synthesized capsid proteins (NP and polymerase complex proteins) are transported by this time. [26]



Entrance of influenza virus into the host cell

Pathogenesis

Usually the entrance gate of infection is the upper respiratory tract, but the virus can penetrate directly into the alveoli, which causes the development of pneumonia. The primary reproduction of viruses occurs in the epithelial cells of the respiratory tract. Infected cells begin to produce interferon, which has a nonspecific antiviral effect. Inflammation, edema, swelling of the basement membrane develop, desquamation of cells of the superficial epithelium occurs. The influenza A virus enters the bloodstream through damaged epithelial barriers and causes viremia. The absorption of cellular debris also has a toxic and sensitizing effect on the body. The virus activates the proteolysis system and causes damage to the capillary endothelium. This increases the permeability of blood vessels and serous membranes, which causes hemorrhages and hemodynamic disturbances

with microcirculation disorders. With influenza, transient secondary immunity also develops, which predisposes to secondary bacterial infection. [27]

Clinical presentations

The incubation period for influenza is short - 1-3 days. The disease begins acutely with the onset of chills and an increase in temperature to 38.5 - 40.0 'C during the first day. Influenza is characterized by a rapid rate of development of clinical symptoms. Already in the first 2 days from the onset of the disease, there is usually a detailed picture of the disease, in which the phenomena of general intoxication prevail. One of the most persistent symptoms of a febrile period observed in older children is headache localized in the frontotemporal region. At the same time, patients complain of pain in muscles, joints, and eyeballs. General weakness is characteristic, which lasts throughout the entire disease, often persisting during the period of convalescence. Reduced appetite. In some patients, vomiting is observed. At the height of the fever, convulsions may occur. Possible short-term impairment of consciousness. In some patients, meningeal signs may be detected.

The skin is usually pale; in older children, the cheeks may be hyperemic. The vessels of the conjunctiva of the eyelids and sclera are sharply injected. Hemorrhagic syndrome, which develops with severe toxicosis, manifests itself in the form of nosebleeds, punctate hemorrhages on the skin and mucous membranes, microhematuria. A dangerous manifestation of this syndrome is the development of hemorrhagic pneumonia.

Simultaneously with the symptoms of toxicosis, from the first day of illness, catarrhal phenomena appear from the upper respiratory tract. Most patients develop rhinitis, manifested by hyperemia and swelling of the nasal mucosa, then small serous and serous-mucous discharge appears. Almost all patients show characteristic changes in the oropharynx. Usually there is a sharp hyperemia and swelling of the soft palate, arches, uvula, tonsils, posterior pharyngeal wall, profuse granularity.

The development of tracheitis is typical for influenza, and cough is one of the most persistent symptoms of the disease. The cough is often dry, often painful, raw, some patients note pain behind the sternum, along the trachea. Isolated laryngitis with influenza is rare and is manifested by hoarseness, aphonia. Laryngotracheitis is more common, which can lead to stenosis of the larynx and the development of croup syndrome.

From the side of the lower respiratory tract, dry wheezing can be heard for a short time. Breathing in the lungs is vesicular, sometimes harder.

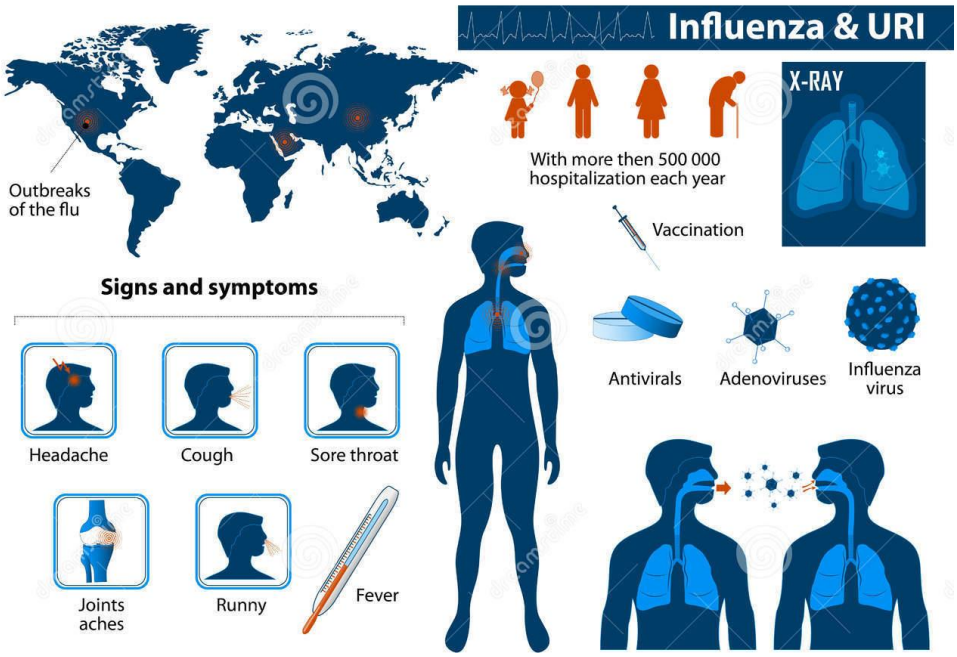
From the side of the cardiovascular system, tachycardia is noted. The pulse rate usually corresponds to the temperature. The liver and spleen are not enlarged.

Fever with influenza lasts for different periods - from 2 to 5 days, rarely longer - and is reduced by accelerated lysis, while sweating is noted. Catarrhal phenomena can persist a little longer and disappear after 10-14 days.

In each patient, the severity of clinical manifestations, the severity of the course of the disease are different. Some symptoms may be absent or mild, but the typical features of influenza infection usually persist. Young children and patients with chronic broncho-pulmonary and cardiovascular diseases, diabetes mellitus should be included in the high-risk group for a severe course of influenza.

Influenza has some clinical features in newborns and in children during the first 3-5 months of life. They do not have such an intense, rapid development of symptoms; their disease develops more slowly and lasts longer. Body temperature is usually not as high as in older children. Fever may sometimes be absent. The onset of the disease is not always clearly indicated. However, despite the low severity of the main manifestations of the disease, influenza in children of this age is very dangerous and often gives complications that can develop catastrophically.

Diseases observed in different influenza epidemics, while maintaining typical symptoms, may clinically differ in the severity and frequency of their occurrence, varying severity, number and nature of complications.



[28]

Immunity

The mechanism of anti-influenza immunity is associated with natural factors of antiviral nonspecific defense, mainly with the production of interferon and natural killer cells.

Specific immunity is provided by the factors of cellular and humoral response. The former are represented by macrophages and killer T cells. The second are

immunoglobulins, primarily antihemagglutinins and antineuraminidase antibodies, which have virus-neutralizing properties. The latter, in contrast to antihemagglutinins, only partially neutralize the influenza virus, preventing its spread. Complement-binding antibodies to viral nucleoprotein do not have protective properties even after 1.5 months. disappear from the blood of convalescents.

Antibodies are detected in blood serum 3-4 days after the onset of the disease and reach maximum titers in 2-3 weeks. The duration of specific immunity acquired after influenza infection, contrary to previous ideas, is measured in several decades. This conclusion was reached on the basis of a study of the age structure of the incidence of influenza caused by the A (H1N1) virus in 1977. It was found that this virus, which had been absent since 1957, in 1977 only affected persons under 20 years of age.

Thus, after the transfer of influenza infection caused by the type A influenza virus, a tense immunity is formed, strictly specific to the subtype of the virus (for H and N antigens) that caused its formation.

In addition, newborns have passive immunity due to IgG antibodies to the corresponding subtype of virus A. Immunity lasts for 6-8 months. [14]

Diagnostics

Diagnostic methods	Express diagnostics	Virological method	Serological methods
Research material	Nasopharyngeal discharge, smears from the nasal mucosa	Isolation of the influenza virus during infection with virus-containing material (washings from the nasopharynx in the first days of the disease) of chicken embryos or cell cultures.	Paired serum from the patient with an interval of 10-14 days: at the onset of the disease and during the recovery period.

Detection methods	ELISA, PCR	HI test, CFT, ELISA, SVN assay	CFT, HIT, ELISA, SVN assay
Revealing	Viral antigen, virus RNA	Viral antigen	Increase in antibody titer (4-fold increase in antibody titer)

Treatment

As a rule, symptomatic and pathogenetic therapy is used in the treatment of influenza, which includes antipyretic, vasoconstrictor, antihistamines, vitamins, detoxification, immunomodulators, angioprotectors, proteolysis inhibitors, etc.

Intranasally, interferon a is administered, which has an antiviral effect.

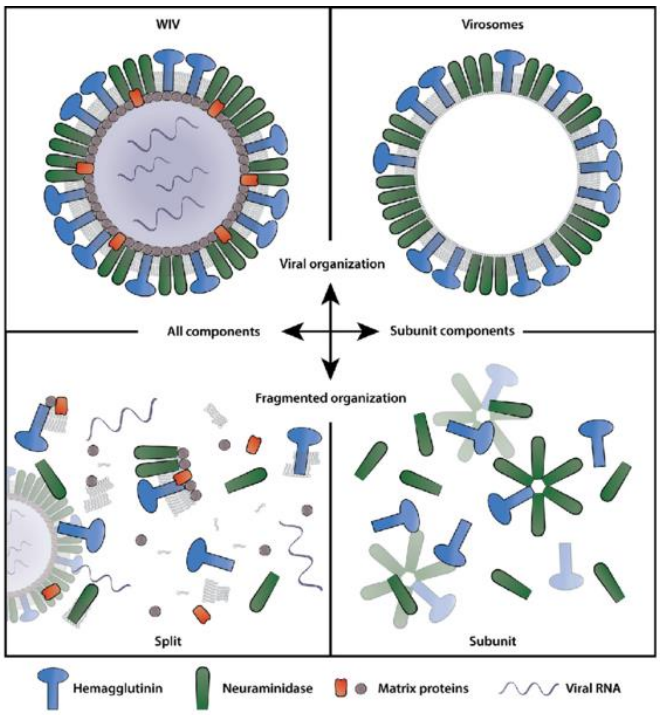
In the first 48 hours, various antiviral chemotherapeutic drugs are used: rimantadine - inhibits the reproduction of influenza A viruses only by blocking the ion channels of the M2 protein, arbidol - acts on influenza A and B viruses; oseltamivir is a neuraminidase inhibitor.

Prevention

Prevention of influenza is non-specific and specific.

For non-specific prophylaxis, anti-epidemic measures are carried out aimed at limiting the spread of influenza viruses by aerogenic and contact (isolation of patients, quarantine, disinfection of linen and dishes, thorough washing of hands, wearing masks, etc.) It is also important to increase the overall resistance of the body. For nonspecific antiviral prophylaxis, preparations of α-interferon and oxolin are used intranasally, and neuraminidase inhibitors, arbidol, rimantadine are used for emergency chemoprophylaxis.

Specific routine prophylaxis consists of vaccines. It is important to vaccinate at least 1 month before the beginning of the epidemic season (September, October), in order to form an active immunity. Vaccination is recommended primarily for children, people from a high-risk group, health care personnel, etc. Currently, there are live vaccines, inactivated whole virion vaccines, chemical, split - vaccines.



Inactivated influenza vaccine options *[29]*

[30]

[31]

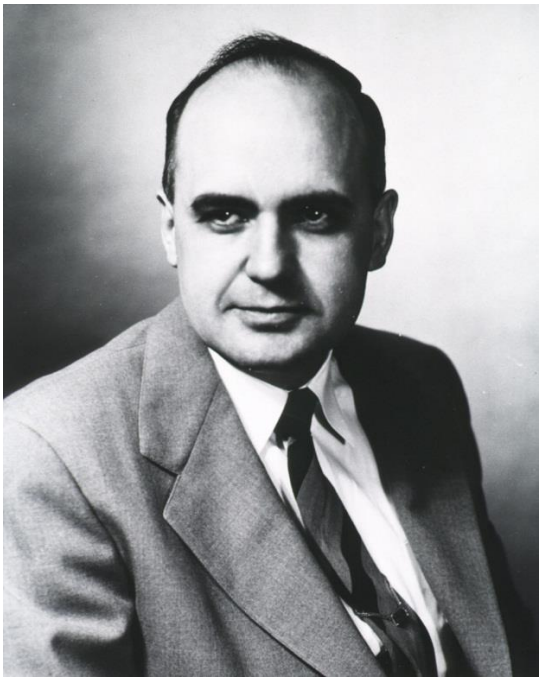
Adenovirus

Adenovirus infection is an acute anthroponous viral infection that affects the mucous membranes of the upper respiratory tract, eyes, intestines, lymphoid tissue and proceeds with moderate intoxication. [32]

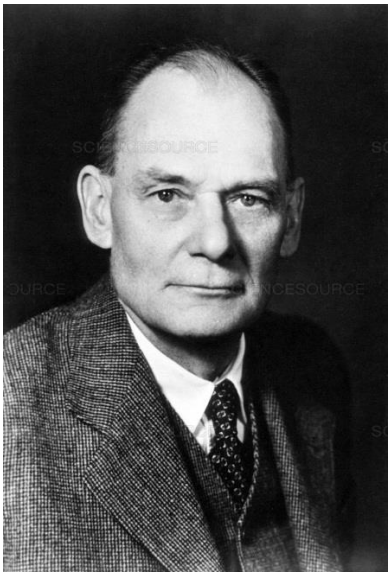
Historical background

In 1953, in the laboratory of R. Huebner (USA), W. Rowe discovered the presence of a new previously unknown virus in the adenoid tissue of healthy children. Around the same time, a number of similar viruses were isolated by M. Hilleman, who was studying the etiology of respiratory infections among military personnel. Later F. Neva and J. Enders isolated a similar virus from the intestines of the child, and L. Kjellen from the mesenteric lymph nodes. Further studies have shown that adenoviruses can be isolated from the tissues of the Pirogov-Valdeyer lympharyngeal ring and from the feces of a healthy person of any age.

Based on the commonality of serological properties, these viruses were combined into a single group and subsequently received the name adenoviruses (from the Greek adenos - iron)



M. Hilleman

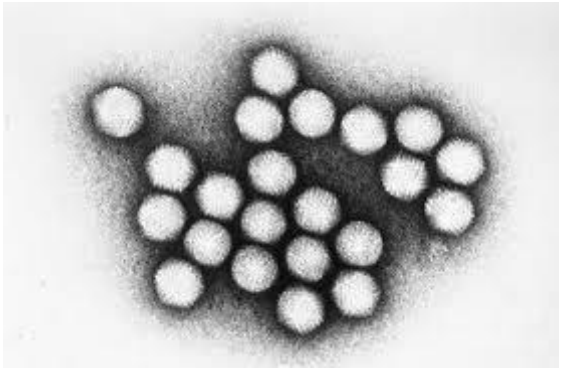


J. Enders

Taxonomy

Adenoviruses belong to the family of the same name Adenoviridae (a family of DNA-containing viruses of vertebrates devoid of lipoprotein envelope), consisting of 5 genera. Numerous adenoviruses of mammals, birds, and fish belong to these genera. Human adenoviruses belong to the genus Mastadenovirus (mammalian adenoviruses, of medical importance). According to the modern classification, this genus includes 36 types of

viruses. The causative agents of human adenovirus infections are represented by 7 species (groups) - human mastadenovirus A-G. Within species, adenoviruses are divided into multiple types, which are assigned a serial number. Initially, typing is carried out by serological methods (RTGA, neutralization test). Currently, the division of adenoviruses into types is based on the genetics (sequencing of the viral genome). At least 67 types of human adenoviruses have been identified. [33]

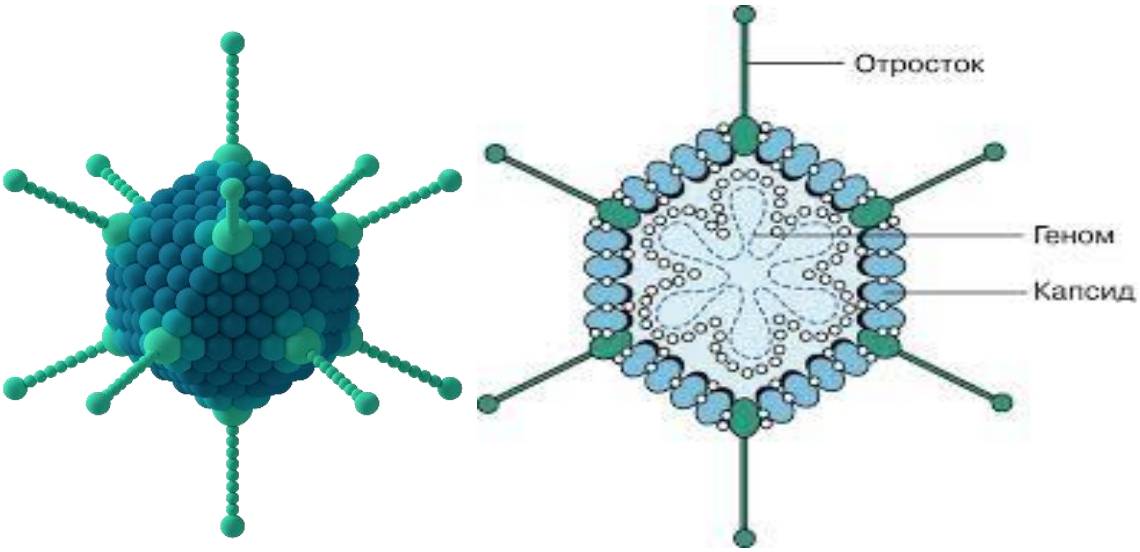


TEM micrograph of adenoviruses [34]

Morphological and tinctorial properties

Representatives of adenoviruses have a spherical virion of average size with a diameter of 70-100 nm. Virions have a cubic type of symmetry, do not have a supercapsid (simple viruses). The viral capsid consists of 252 capsomeres, built according to the icosahedral type of symmetry. Among them, 240 hexons and 12 pentones are distinguished. Lateral capsomers (hexons) have contact with six adjacent ones. Pentones interacting with the five nearest capsomeres-hexons form the capsid apexes. Fibers - glycoprotein fibrils that perform a receptor function - depart from the pentones. They exhibit hemagglutinating activity. Generic, species and type-specific antigens are located in hexons, and type-specific antigens are located in fibers. The outer shell is missed. Adenoviruses are made up of DNA and proteins. The genome of adenoviruses is represented by a linear double-stranded DNA, which binds to proteins and forms a dense core of the virus located under the apex of the capsid. It contains up to 40 genes that determine the synthesis of viral proteins and regulatory RNAs. In animal experiments, it was found that certain genes of adenoviruses have the properties of oncogenes and can cause tumors in various mammalian species. During the reproduction of adenoviruses, primary RNA transcripts undergo alternative splicing to form several mRNAs encoding viral proteins.

Early and late adenoviral proteins are isolated. Among them are proteins-enzymes (DNA polymerase, protease); numerous regulatory proteins that control the processes of transcription of the viral genome; structural proteins that form the viral capsid. A number of proteins act as virulence factors in the infectious process. The receptor proteins of adenoviruses are found in the fibers. During infection, they interact with receptors in cell membranes and activate the penetration of the virus. Certain proteins of adenoviruses inhibit apoptosis of infected cells and suppress antiviral immunity (disrupt the presentation of AH by HLA class I molecules, reduce the activity of NK cells and T-lymphocytes, inhibit the secretion of cytokines - interferons, TNF). [33]



Adenovirus. [35]

Cultural properties

Adenoviruses do not multiply in chicken embryos, but they multiply well in primary-trypsinized and transplanted cell cultures of various origins, causing a characteristic cytopathic effect (rounding of cells and the formation of gravel-like clusters from them, small-point degeneration). [36] Adenoviruses are adsorbed on cell receptors using filaments. Deproteinization of virions that have entered the cell begins in the cytoplasm and ends in the nucleus, where DNA with a terminal protein attached to it is released. [37] Then, with the help of cellular enzymes, the genome is transcribed and the viral DNA is replicated. The assembly of viral particles takes place in the nucleus. At the same time, several hundred viral particles are synthesized in each cell. When the adenovirus exits, the host cell is destroyed.

Resistance

Adenoviruses are highly resistant to external influences. They remain viable in the environment for several weeks at room temperature, at 4 ° C for several months. They can be on various surfaces and household items for 3 months. In the water of open reservoirs and sewage they are stored for weeks. Viruses lose their viability when incubated for 30 min at 56 ° C and within 2 min at 60 ° C; are inactivated by ultraviolet radiation. Sensitive to chlorine-containing disinfectants, formaldehyde, resistant to ether, detergents.

Epidemiology

The source of infection is patients with acute or latent adenovirus infection. Infection occurs by airborne, contact-household, fecal-oral route. Adenoviruses cause sporadic diseases and localized epidemic outbreaks. Adenovirus infections more often affect children from 6 months up to 2 years.

Virulence factors of the pathogen

Adenoviruses have tropism for many epithelial cells, leukocytes. The fibers of most adenoviruses interact with membrane CAR-receptors (coxsackie adenovirus receptor). In addition, adenoviruses can enter cells by binding to CD46 molecules. Pathogens enter the cytoplasm of cells by endocytosis. Deproteinization of virions is completed near the cell nucleus. Replication of adenoviruses occurs in the nuclei of infected cells. The DNA of viruses enters the nucleus, where it exists as an episome. Integration of viral DNA with the cellular genome is possible, but rarely occurs. Viral RNAs are synthesized by the enzyme cellular RNA polymerase II from the templates of both DNA strands. After splicing, 239 mRNAs are translated on ribosomes to form early and late viral proteins. The early proteins mainly serve the replication of viral DNA, while the late ones are part of the capsid. Replication of genomic DNA is carried out by viral DNA polymerase. The assembly of the virus takes place in the nucleus with the participation of the viral protease. The release of adenoviruses is accompanied by swelling, aggregation, and less often by lysis of infected cells. The formation of a latent infection is possible. The duration of the reproductive cycle of adenoviruses is about 24 hours.

Pathogenesis

By the type of lesions of sensitive cells, there are 3 types of infections:

1. Productive infection - accompanied by cell death after the next population of virions leaves it (up to 1 million virions). But at the same time, only 1-5% of virions are infectious.

2. Persistent infection - occurs when the rate of reproduction of the virus slows down, this allows the cells to repair the damage caused by the virus, and the tissues replenish the loss of infected cells by dividing uninfected cells. This form of infection is asymptomatic and chronic.

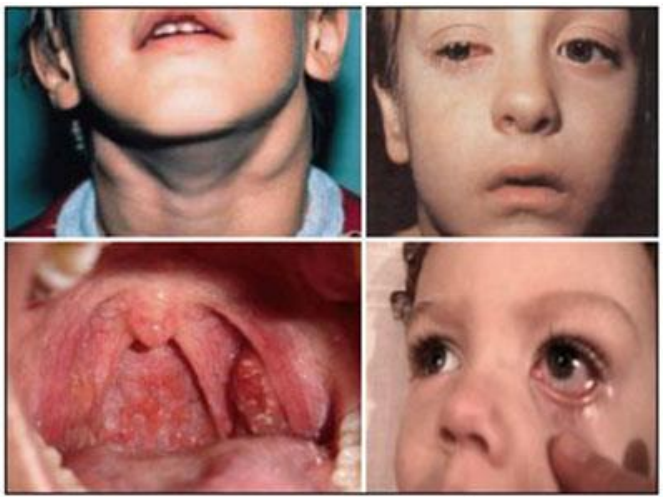
3. Transforming infection - occurs when newborn mice, rats, hamsters are infected with human adenoviruses. They develop tumors. [37]

Clinical presentation

The incubation period is 5 to 14 days. Adenovirus infection is characterized by polymorphism of clinical manifestations. In the clinical picture, symptoms may predominate, indicating damage to the respiratory tract, eyes, intestines, bladder, and lymphoid tissue, and meningoencephalitis may develop. In most cases, symptoms of intoxication are mild, even with high fever. The temperature rises from the first days of the illness, its duration can vary from 5-7 days to 2 weeks. Sometimes subfebrile condition persists up to 4-6 weeks, there may be a two-wave fever, rarely three waves are observed. Due to the tropism of adenoviruses to lymphoid tissue, from the first days of the disease, difficulty in nasal breathing, puffiness of the face, profuse serous-mucous rhinitis (especially in younger children) appear. A characteristic symptom of the disease is pharyngitis with a pronounced exudative component. Pharyngitis is characterized by moderate sore throat or sore throat due to hyperplasia of lymphoid formations against the background of edematous and hyperemic mucous membrane of the posterior pharyngeal wall. The tonsils are enlarged; in some patients, white, delicate, easily removable overlays with a spatula are visible. In most cases, adenovirus infection is accompanied by moderate lymphadenopathy (LAP). The cervical, submandibular, mediastinal and mesenteric LNs increase. The cough is moderate, short-lived, more often in children; clinical signs of bronchitis in adults are quite rare. At the same time, almost every 5th sick child develops acute stenosing laryngotracheitis, which is difficult, with a pronounced exudative component. Some sick children have obstructive syndrome, which has an edematous or mixed form, which can persist for up to 3 weeks. At the same time, the cough is wet, obsessive, exhalation is difficult, shortness of breath is of a mixed type. Auscultatory is determined by a large number of different-sized wet and single dry wheezing. Young children may develop bronchitis, bronchiolitis. There are practically no changes in the cardiovascular system. Some patients have

hepatolienal syndrome, sometimes with an increase in the level of transferases (ALT, AST). Mesenteric infection manifests itself either against the background of other manifestations of adenovirus infection, or as the main syndrome. The main clinical sign in this case is acutely arising severe, paroxysmal pain in the abdomen, mainly in the lower part, often in the right iliac region, sometimes in the umbilical region. Nausea, there may be vomiting, diarrhea. The overwhelming majority of patients have conjunctivitis. At first it is unilateral, the second eye is affected later. Distinguish between catarrhal, follicular and membranous conjunctivitis. The latter form is particularly typical. The conjunctiva of the eyelids is hyperemic, granular, somewhat swollen; there may be a slight highlighting of the secret. After 1-3 days, white or grayish-white filmy deposits appear on the conjunctiva. A common symptom is swelling of the eyelids. In adult patients with adenovirus infection, there may be clinical signs of hemorrhagic cystitis. There are observations of the development of acute encephalitis. Among the various serotypes of adenoviruses in connection with acute encephalitis, the 7th serotype is most often mentioned. Pharyngo-conjunctival fever, which has a fairly clear clinical picture with a high 4-7-day temperature, general toxic syndrome, rhinopharyngitis, membranous conjunctivitis, has been identified as an independent form of the disease.

Young children have gastroenteritis caused by adenoviruses. Meningoencephalitis and hemorrhagic cystitis are rare. [38]



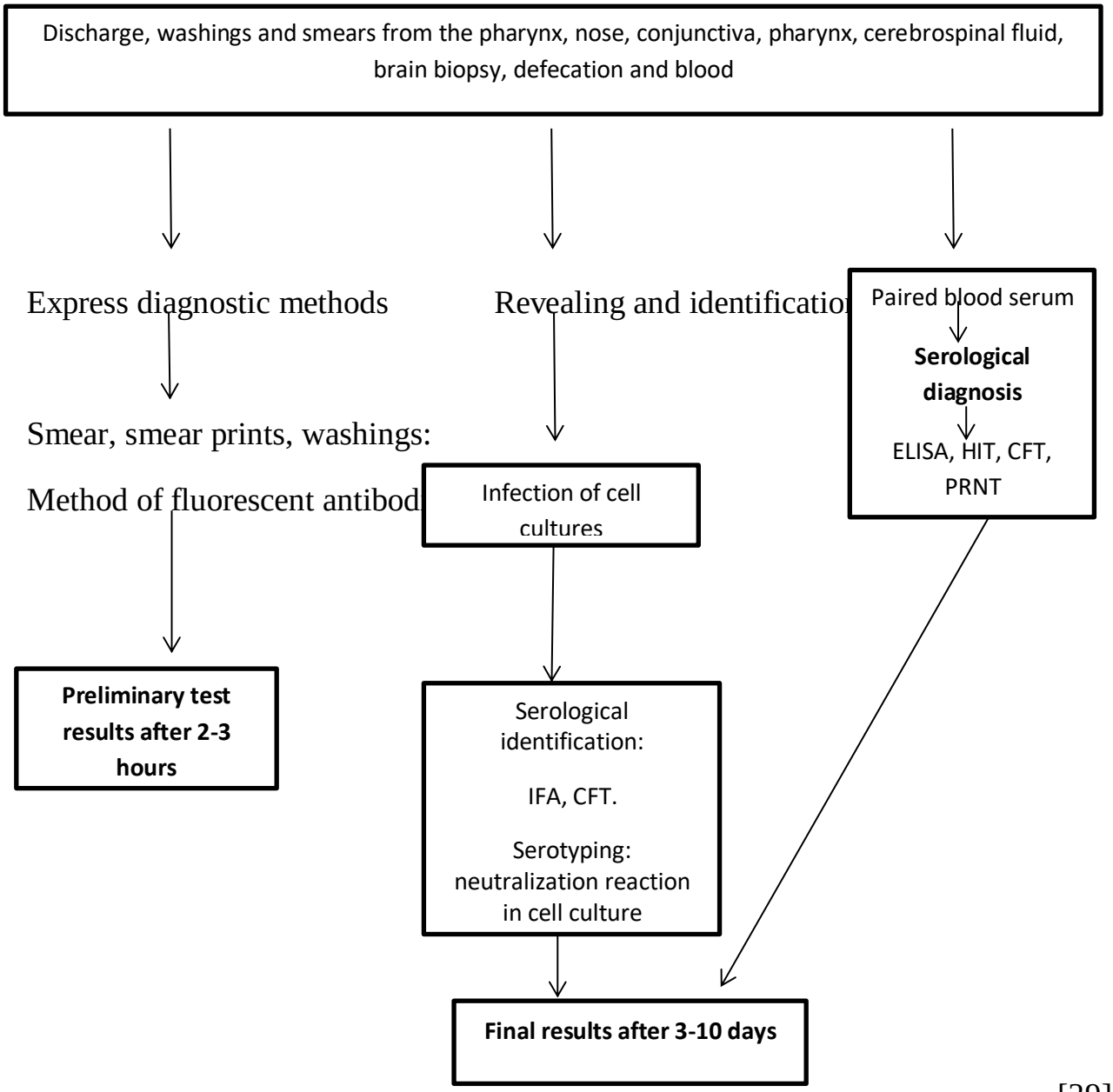
Adenovirus infection

Immunity

After a disease, patients develop a short-term type-specific immunity, which is of a cellular-humoral nature.

10. Diagnostics

Microbiological diagnosis of adenovirus infections



[39]

Treatment

Treatment is symptomatic, bed rest, drinking plenty of fluids, antipyretic drugs. Most patients are treated at home. Patients with a severe form of the disease, in the presence of complications, concomitant diseases, and also for epidemic indications are subject to hospitalization. In a febrile period, bed rest is necessary. Meals should be complete and rich in vitamins, contain a sufficient amount of liquid. Most patients with an uncomplicated form of adenoviral disease do not need etiotropic therapy. With pronounced motivation of the patient and with a severe course of the infectious process, umifenovir (Arbidol), IFN preparations and their

inducers are indicated. Among natural IFNs the following can be used: IFN-α (human leukocyte interferon) (aerosolized), interlock (for the treatment of conjunctivitis), IFN-α (Leukinferon) (injected intramuscularly, by inhalation) 100 thousand IU. Recently, preparations of recombinant interferon, the safest in comparison with leukocyte interferon, have been widely used. IFN-α2 recombinant is a part of topical preparations: drops and spray Grippferon, nasal ointment Grippferon with loratadine. IFN content - 10 thousand IU. Antibiotics are indicated only for pneumonia and other complications of a bacterial nature. Symptomatic therapy according to indications. The prognosis is usually good. [38]

Prevention

In the prevention of adenoviral diseases, the main role belongs to non-specific preventive measures that increase the body's resistance to infectious diseases: adherence to the daily regimen, hardening, balanced nutrition, healthy sleep, sufficient physical activity, etc.

During epidemic outbreaks, interferon is prescribed to contact persons for prophylactic purposes.

In the focus of infection, current disinfection is carried out.

During outbreaks of adenovirus infections, children are separated for a period of at least 7 days after the last case is identified.

A person with adenoviral infection should be isolated in a separate room, have a separate towel, separate dishes, which must be further boiled or disinfected with disinfectants.

Those in contact with an adenovirus infection should use barrier methods of prevention - medical masks and respirators.

Important in the prevention of adenovirus infection is adherence to the rules of personal hygiene:

• regular hand washing, as well as the use of antiseptics when it is not possible to wash your hands

• prevention of the spread of infection when sneezing and coughing using disposable handkerchiefs

• exclusion of touching the face with dirty hands

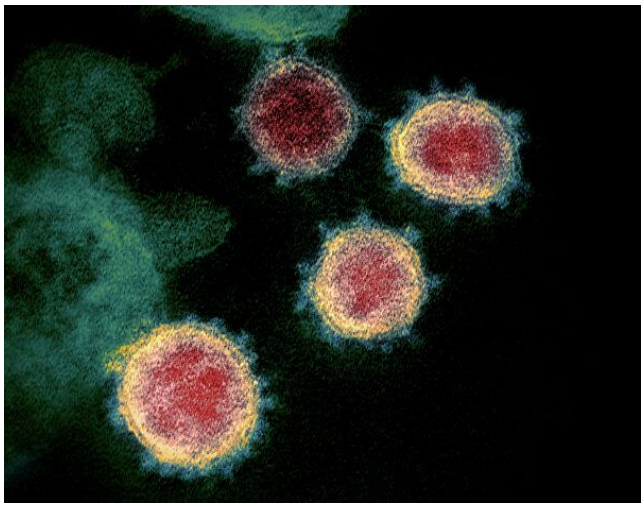
• exclusion of close contacts[42]

Vaccines for specific prophylaxis have been developed, but due to their oncogenic properties, they have not received practical use.

Coronavirus

Historical background

Coronavirus infection (COVID-19, abbreviation from the English Corona VIrus Disease 2019) is an acute infectious disease caused by a new strain of SARS CoV-2 coronavirus with aerosol droplets and contact-household transmission mechanism.



Coronavirus under a microscope

The human coronavirus was first isolated in 1965 from a patient with acute respiratory illness. Various types of coronaviruses are widespread in nature,

causing various infectious pathologies in animals. Now the family of coronaviruses includes more than 30 species. It is constantly updated.

In the 20th century, coronaviruses were known as causative agents of acute respiratory diseases in humans and animals, but they were not among the most dangerous viral infections. Currently, the coronavirus family includes two types of viruses that cause severe respiratory infection in humans: SARS-Cov (Severe acute respiratory syndrome coronavirus, or SARS coronavirus, which causes severe acute respiratory syndrome) and MERS-Cov (Middle East respiratory syndrome coronavirus, or MERS coronavirus causing Middle East respiratory syndrome).

The SARS coronavirus caused an epidemic in 2003 in 33 countries of the world (the largest number of cases was recorded in China, Singapore and Canada), with a total of 7,761 people, of whom 623 were fatal. The SARS-Cov virus is easily transmitted from person to person. Since September 2012, cases of a new infection caused by the MERS-Cov coronavirus have been registered in the Middle East, the mortality rate according to WHO is about 43%. It is believed that human infection occurs through contact with camels or with virus-infected environmental objects in the household, as well as when visiting livestock farms. The possibility of MERS-Cov transmission from person to person through close and prolonged contact has been confirmed, which can provoke outbreaks of nosocomial infection in the human population. Bats are the natural reservoir for both viruses.

At the end of December 2019, Chinese authorities reported an outbreak of pneumonia of unknown origin in Wuhan. The first cases were related to the seafood market. Experts have previously established that the causative agent of the disease was a new type of coronavirus - 2019-nCoV. [43]

The COVID-19 pandemic is the current coronavirus infection pandemic caused by the SARS-CoV-2 coronavirus. The outbreak was first reported in Wuhan, China in December 2019. The outbreak was declared a public health emergency of international concern by the World Health Organization on January 30, 2020, and a pandemic on March 11. As of December 31, 2020, the pandemic had more than 83.2 million cases worldwide; more than 1.815 million people died and more than 59.29 million recovered.

The COVID-19 pandemic has caused serious socio-economic consequences including the largest global recession since the Great Depression and massive famine, affecting about 265 million people. This has led to the postponement or cancellation of many sporting, religious, political, and cultural events, and widespread supply shortages have been exacerbated by panic buying. Decreased emissions of pollutants and greenhouse gases. Schools, universities and colleges have been closed either nationwide or locally in 172 countries, affecting approximately 98.5% of the world's school and student age population. [44]

Disinfection of the street in Taiwan [45]

The first cases of coronavirus infection COVID-19 were registered in Kazakhstan on March 13, 2020. According to official statistics, as of October 31, 136,271 cases of infection were registered in Kazakhstan, 118,643 patients recovered, 2067 patients could not be saved. 15543 people were hospitalized with the diagnose COVID-19.

To prevent the spread of the disease, from March 16 to May 11, 2020, a state of emergency was introduced in the country: restrictions on entry and exit from the country were imposed, quarantine or other restrictive measures were introduced in all regions, the activity of large non-food trade facilities, cinemas and others was ceased where places with a mass gathering of people.

On July 5, 2020, a strict isolation regime began to operate in Kazakhstan. All facilities were closed, except for grocery stores, pharmacies, cafes (while maintaining social distancing), airports (domestic flights).

On July 8, 2020, the President of Kazakhstan, Kassym-Jomart Tokayev, declared July 13 as the day of national mourning for those who died due to the coronavirus COVID-19. [46]

Taxonomy

Coronaviruses (lat. Coronaviridae) are a family of protein deficiency viruses (nsp designation), which as of May 2020 includes 43 types of RNA-containing viruses, combined into two subfamilies that infect mammals (including humans), birds and amphibians. The name is associated with the structure of the virus, the spines of which resemble the solar corona. There are 7 known coronaviruses that infect humans:

• HCoV-229E - Alphacoronavirus, first identified in the mid-1960s;

• HCoV-NL63 - Alphacoronavirus, the causative agent was identified in the Netherlands in 2004;

• HCoV-OC43 - Betacoronavirus A, the causative agent was identified in 1967;

• HCoV-HKU1 [ru] - Betacoronavirus A, the causative agent was found in Hong Kong in 2005;

• SARS-CoV - Betacoronavirus B, the causative agent of severe acute respiratory syndrome, the first case of which was reported in 2002;

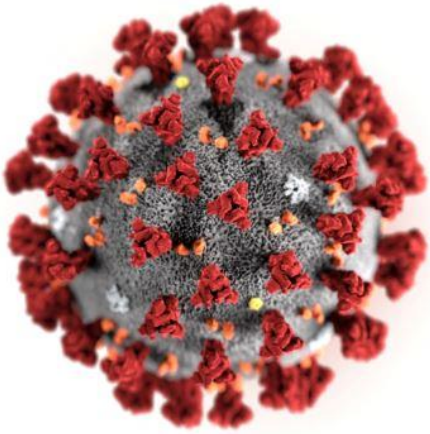
• MERS-CoV - Betacoronavirus C, the causative agent of the Middle East respiratory syndrome, the outbreak of which occurred in 2015;

• SARS-CoV-2 - Betacoronavirus B, detected in the second half of 2019, which caused a pandemic of a new type of pneumonia COVID-19, and by the spring of 2020 became a worldwide problem, as a result of which many borders were closed and emergency security measures were introduced (quarantine, strict isolation and so on). [47]

Morphological and tinctorial properties

Large virions are particles with a diameter of 60-130 nm, spherical. Nucleocapsid of helical symmetry, contains single-stranded RNA-plus, is covered with a lipid membrane - supercapsid. On the supercapsid, there are characteristic clavate projections in the form of a solar crown - peplomeres, on which antigenic determinants are located. At the site of attachment to the viral envelope, peplomeres form a narrow isthmus.

The main phosphoprotein N, which forms the nucleocapsid structure, is associated with the virus genome. In the membrane, multimembrane protein M and glycoprotein S are found, in the envelope - protein E. In some coronaviruses, the presence of hemagglutinin esterase is noted. Glycoprotein S, a signaling protective antigen in SARS, is an inducer of virus neutralizing antibodies. When coronaviruses enter the body, agglutinating, precipitating antibodies are produced. [48]



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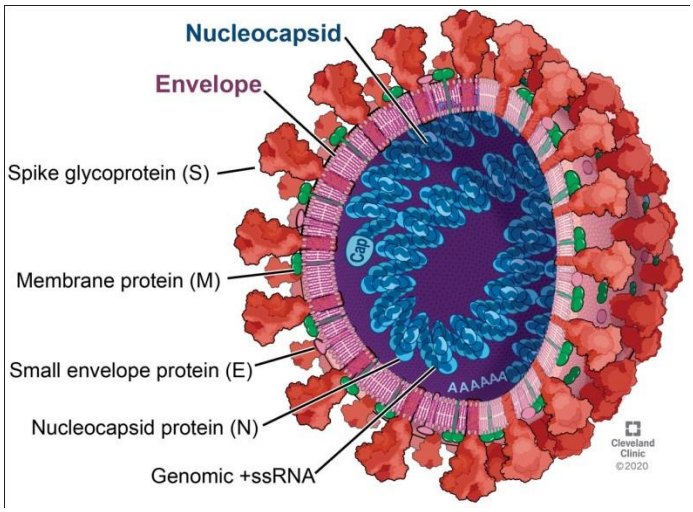


The structure of coronavirus [50]

Cultural properties

Coronaviruses reproduce in the cytoplasm of human and animal cells - their natural hosts. It is possible to use cultures of human embryonic cells and primary epithelial cells. The optimum temperature for cultivation is 33-35C. Intracellular inclusions are not formed. [51]

Resistance

The resistance of the virus on different surfaces is different and depends on the temperature. On paper, the virus is destroyed in 3 hours, on banknotes in 4 days, on wood and clothing in 2 days, on glass in 4 days, on metal and plastic in 7 days. On the inner layer of the used mask in 7 days, and on the outer surface of the mask it remains for more than 7 days. The data correspond to +22 ° C and humidity 65% .

Coronaviruses remain infectious for several years in a lyophilized state at + 4 ° C, that is, after mild drying in a laboratory after preliminary freezing. In a frozen state at -70 ° C, coronaviruses have also been successfully stored in laboratories for several years. In the external environment, coronaviruses are usually inactivated from surfaces at +33 ° C in 16 hours, at +56 ° C for Special studies on the causative agent COVID-19 showed that, in general, it reacts to antiseptics in the same way as other coronaviruses. Ethanol (70%), chlorhexidine (0.05%), chloroxylenol (0.05%), benzalkonium chloride (0.1%), povidone-iodine (7.5%) destroyed the virus within 5 minutes. Standard methods of disinfection of premises using chlorine-containing antiseptics at a concentration of even 1:99 also killed the virus within 5 minutes and 10 minutes. [52]

Epidemiology

Bats are currently the natural reservoir of the SARS-CoV-2 virus. Studies have shown that mammals that eat bats can serve as an additional reservoir, with further distribution among humans. Phylogenetic studies of the isolated strains have shown that the genomic sequences of viruses found in bats are 99 percent identical to those isolated from patients with COVID-19. AT THE PRESENT TIME, THE MAIN SOURCE OF INFECTION IS A SICK PERSON, INCLUDING IN THE INCUBATION PERIOD OF THE DISEASE. As a rule, transmission of infection is carried out by airborne droplets (when coughing, sneezing, talking). The contact-household route is realized through transmission factors: water, food products and objects contaminated with the pathogen. The risk of transmission of the virus from the hands to the mucous membranes of the eyes, nose and mouth and the disease has been proven. It is possible to implement the fecal-oral mechanism (the pathogen was found in fecal samples from patients infected with SARS-CoV-2). [53]

Virulence factors of the pathogen

• Coronavirus type 2, which causes severe acute respiratory syndrome (SARS-CoV-2), binds to ACE2 receptors in humans, thus the pathogenesis of the disease is similar to that of severe acute respiratory syndrome.

• The unique structural feature of the SARS-CoV-2 spine glycoprotein receptor-binding domain (which is responsible for the entry of the virus into host cells) provides a potentially higher binding affinity for ACE2 with host cells compared to SARS-CoV-1. Other SARS-like coronaviruses have no furin-like cleavage site. The binding energy between the spike protein and ACE2 of all the studied species was the highest in humans, which indicates that the SARS-CoV-2 spike protein has

evolved in a unique way and is now able to bind to human cells expressing ACE2 and infect them.

• Data on the mechanism of action of other coronaviruses suggests that SARS-CoV-2 may decrease the number of ACE2 receptors, leading to toxic excessive accumulation of angiotensin-II in plasma, which can cause acute respiratory distress syndrome and fulminant myocarditis.

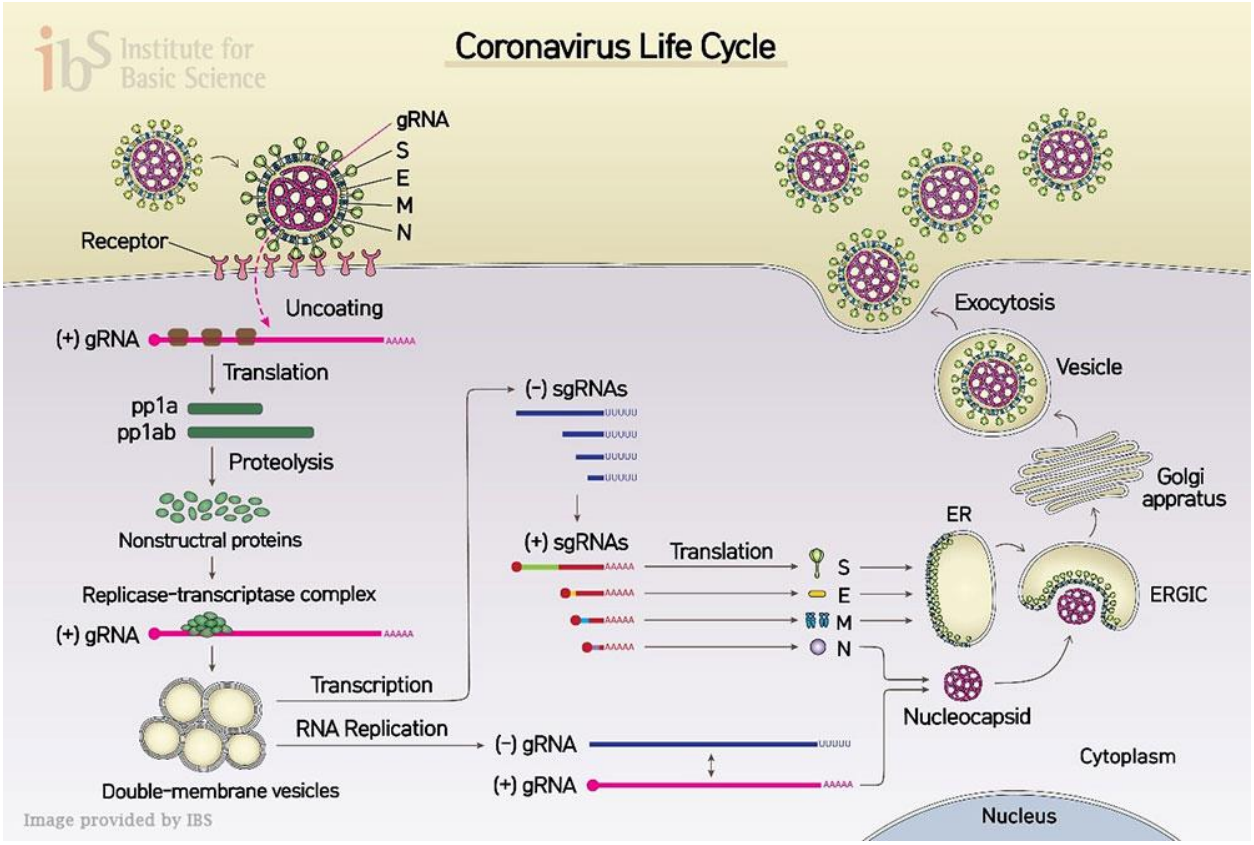
• Based on the analysis of single cell RNA sequencing datasets obtained from basic human physiological media, organs more vulnerable to SARS-CoV-2 infection, due to their levels of ACE2 expression, are the lungs, heart, esophagus, kidneys, bladder and the ileum. This may explain extrapulmonary manifestations associated with infection.

• The lower expression of ACE-2 in the nasal epithelium of children <10 years of age compared to adults may explain why COVID-19 is less common in children, but further research is needed.

Transmembrane Serine Protease 2 (TMPRSS2)

• SARS-CoV-2 uses the host TMPRSS2 for the S-protein primer and the fusion of the viral and host cell membranes.

• Higher expression of TMPRSS2 has been noted in the nasal epithelium of blacks compared with Asians, Hispanics, Whites, and people of mixed race / ethnicity, which may be a contributing factor to the higher infection burden in Blacks. [55]



[56]

Coronavirus life cycle diagram. Having penetrated into the cell, the virus releases its RNA, on which ribosomes - cellular machines for protein synthesis - collect viral proteins necessary for the formation of membrane vesicles and for the synthesis of the plus-strand of genomic RNA - gRNA. Viral proteins appear on the auxiliary membrane vesicles, forming the RTC - replication transcription complex, this complex performs replication (duplication of the viral genome) and transcription - synthesis of short subgenomic RNAs (cRNAs) intended for the assembly of structural viral proteins. Structural protein N combines with genomic RNA to form the viral nucleocapsid (genome plus capsid protein). On the endoplasmic reticulum, other structural proteins are synthesized that organize the lipid membrane of the virus.

Pathogenesis

Pathogenetically, COVID-19 is characterized by viremia, local and systemic immune-inflammatory process, hyperactivity of the coagulation cascade, endotheliopathy, hypoxia, which leads to the development of micro- and macrothrombosis; proceeds from asymptomatic to clinically severe forms with intoxication, fever, damage to the endothelium of blood vessels, lungs, heart, kidneys, gastrointestinal tract, central and peripheral nervous systems with the risk of complications (ARF, ARDS, PE, sepsis, shock, SPON).

The main target of SARS CoV-2 is the lungs. In pathogenesis, 2 mechanisms should be distinguished that mutually burden each other and can lead to the development of ARDS (pathomorphologically - diffuse alveolar damage): direct viral damage to alveocytes with the development of immuno-inflammatory syndrome;development of micro- and macrothrombosis of the vessels of the lungs and obstructive thrombo-inflammatory syndrome.

Therefore, the disease was named microCLOTS - microCOVID Lung Obstuctive Trombovascular Syndrome

The severity and severity of the clinical manifestations of COVID-19 depends on the massiveness of the infection (the infectious dose of the virus) on the one hand and the individual characteristics of the macroorganism on the other (age, sex, strength of the immune response, the presence of concomitant diseases, risk factors, etc.).

Thus, the viral lung disease caused by SARS CoV-2 is a specific "COVID-19-associated pneumonia" (abbreviated. COVID-19-pneumonia). [57]

Clinical presentations

The incubation period is 2-14 days. Fever (or no fever), general weakness, malaise, sweating, myalgia and body aches, headache, sore throat,

cough (rare dry with a small amount of stubborn sputum, can be painful, paroxysmal), feeling of tightness, burning, pain, compression in the chest (inability to breathe in deeply), taste and smell disorders, diarrhea,

restless behavior (agitation), conjunctivitis (rare), rash (cause clarification required).

In severe cases: shortness of breath (at the time of examination or in the dynamics of the disease), shortness of breath, feeling short of breath, heart palpitations, nausea, vomiting (rarely) abdominal pain pain in the region of the heart, persistent headache, dizziness, urinary retention.

Features of the infection of COVID-19 in elderly and senile people atypical picture of the disease without fever, cough, shortness of breath, delirium, delirium, tachycardia, decreased blood pressure, falls, functional decrease, conjunctivitis, COVID 19 symptoms may be mild and not consistent with disease severity and prognosis

Risk factors for severe and complicated course in adults:

Age over 65

Concomitant BSK (arterial hypertension, CHF, etc.)

Concomitant chronic diseases of the respiratory system (COPD, BA, fibrotic changes in the lungs, etc.)

Endocrinopathies (diabetes mellitus, metabolic syndrome, obesity, etc.)

Immunodeficiency states (oncological, hematological diseases, etc.)

Other severe chronic diseases (CKD, etc.)

Immunity

Currently, the response of the innate immune system in SARSCoV-2-infected patients is very little studied. It is believed that the key manifestation of the activation of innate immunity in COVID-19 is an increase in the total number of neutrophils, an increase in the concentration of IL-6 and C-reactive protein in the blood serum. Lymphocytopenia is a characteristic feature of the severe form of COVID-19.

Reaction of cellular immunity The development of infection associated with the SARS-CoV-2 virus is accompanied by excessive activation of cellular immunity, as evidenced by a sharp increase in the level of representativeness of cells

expressing HLA-DR and CD38 , against the background of a significant decrease in the population of CD4 + and NK cells in peripheral blood of patients. It is believed that a decrease in the content of CD4 + T cells is a characteristic feature of COVID-19 [11, 46]. The level of representation of cytotoxic CD38 + HLA-DR + CD8 + T cells rapidly increases starting from the 7th day of the disease. The pool of these cells decreases only after three weeks of the disease. Cytotoxic CD8 + T cells in COVID-19 produce large amounts (34–54% more than in healthy people) granzymes A and B and perforin. It is believed that a fairly rapid increase in the population of cytotoxic CD38 + HLA-DR + CD8 + T-cells by the 7-9th day of the disease contributes to the sanogenesis of COVID-19 [23]. Patients with COVID-19 have high levels of pro-inflammatory CCR6 + Th17 cells. It is believed that excessive activation of Th17 cells and an extremely high level of cytotoxicity of CD8 + T cells underlie the severity of immune damage to the lung tissue of patients. Also, in patients with COVID-19, a depletion of the Treg cell pool is observed, which predetermines unlimited activation of inflammation mechanisms and postpones the resolution of the inflammatory process.

Reaction of humoral immunity Activation of virus-specific B-cells leads to their differentiation into plasma cells, which sequentially produce specific antibodies of IgM and IgG class. It has been demonstrated that antibody-producing CD3 – CD19 + CD27hiCD38hi cells in COVID-19 in the peripheral bloodstream appear on the 7th day, their number reaches its maximum value on the 8th day of the disease. Changes in the representation of antibody-producing cells are synchronized with fluctuations in the size of the pool of follicular CD4 + CXCR5 + ICOS + PDOS-1 + TFH cells. During the development of COVID-19, there is a gradual increase in the concentration of SARS-CoV-2-binding antibodies of IgM and IgG class in the blood serum from the 7th to the 20th day of illness. It has been demonstrated that SARS-CoV-2-specific IgM class antibodies disappear at the end of the 12th week from the onset of the disease, and the IgG class persists for a long period of time, determining the level of protection against re-infection. The detection of specific antibodies in the serum of an individual underlies the rapid diagnosis of COVID-19. It has been established that the use of recombinant human monoclonal antibodies (CR3022) in patients with acute and severe SARS-CoV-2 plasma infection of people who have had COVID-19 is accompanied by a significant positive clinical effect. [58]

Diagnostics

Laboratory diagnostics of COVID-19 is carried out by methods:

• polymerase chain reaction (PCR)

• enzyme-linked immunosorbent assay (ELISA) using test systems

• express determination (immunochromatographic - screening method of determination (qualitative method),

• general clinical analyzes

Serological testing for SARS-CoV-2

• COVID-19 serological testing can be used to determine if people have previously been infected with SARS-CoV-2.

• Important to determine because polymer chain reaction (PCR) and other rapid tests currently in use detect the presence of viral material that is only found in people who are currently infected

• The first and most urgent is to check the serological test. Serological testing for SARS-CoV-2 Generic antibody is more sensitive for detecting SARS-CoV-2 infection than IgM and IgG. Antibody testing can play a vital role in the following settings:

• for suspected patients at the initial visit or clinically diagnosed patients with unconfirmed RNA testing;

• for a healthy close contact in a quarantine period;

• for patients with confirmed RNA, seropositive indicates that a specific immune response has been induced. Express testing by immunochromatography based on the principles of enzyme-linked immunosorbent assay (ELISA)

• 1. Express testing for COVID-19 is performed by immunochromatography based on the principles of enzyme-linked immunosorbent assay (ELISA) with the determination of IgG / IgM antibodies to the SARS-COV-2 coronavirus ...

• 2.Material for the detection of IgG / IgM antibodies to SARS-COV-2 coronavirus is a capillary blood sample.

Algorithm of testing for COVID-19 • 6. Express - testing is performed:

• 1) at bedside testing in a hospital (POCT);

• 2) in specially designated and equipped vehicles;

• 3) ambulance teams or mobile mobile teams at home;

• 4) in specialized tents or mobile points of the fence (SP or mobPZB);

• 5) at road and rail crossings (checkpoints);

• 6) in specially designated and equipped points for sampling biomaterial, performing only this study. Testing algorithm for COVID-19

•7. Self-testing is allowed for medical personnel.

• 8. Sampling of biomaterial is carried out by a trained health worker using PPE (medical mask, caps, disposable gloves, if necessary, face shields or glasses, clean, non-sterile, disposable moisture resistant gown).

• 9. Tools and materials for sampling biomaterial and testing:

• 1) express test, including a disposable sterile pipette for capillary blood sampling and buffer solution;

• 2) alcohol wipes;

• 3) disposable scarifier.

COVID-19 testing algorithm

•. After the set exposure time, the tester reads the result. Typically, the exposure time is 15 minutes, but this time may vary depending on the test systems used.

• Exposure time is timed. Excessive exposure time is not allowed, as in this case the result may be invalid !. Interpretation of the research result:

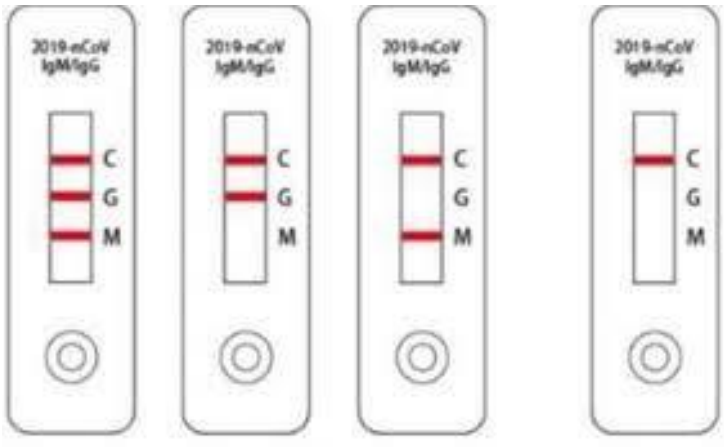
• 1) positive IgM - presence of antibodies, acute period of infection;

• 2) positive IgG - the presence of antibodies, previous disease;

• 3) positive IgM and IgG - transition from the acute stage to the state of the transferred infection;

• 4) positive C (control) - an indicator of the presence of a reaction, a negative result.

• 5) negative C (control) - insufficient sample volume or violation of testing technique. The result is not considered.



Algorithm of testing for COVID-19

• 26. Upon receiving a positive result of the IgM express test, the specialist who conducted the study:

• 1) notifies the tested person about the presence of suspicion of COVID-19 and conducts repeated express testing;

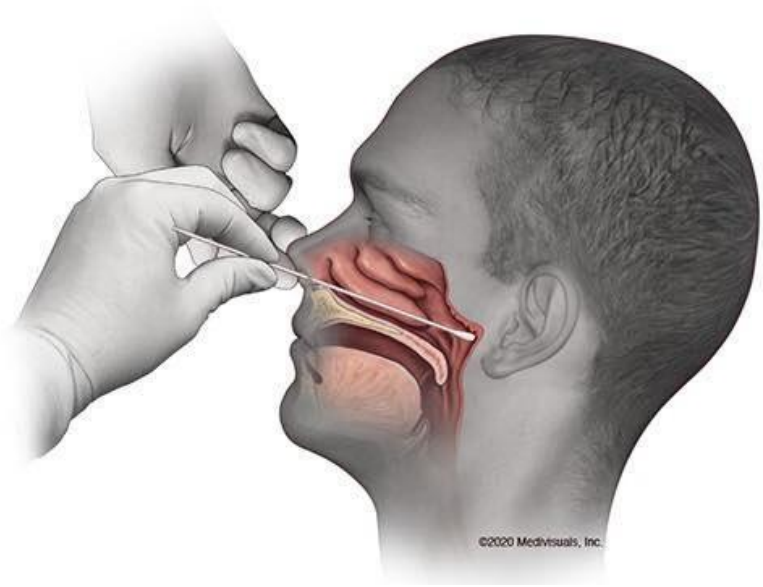
• 2) upon receiving a repeated positive IgM, notifies the head of a medical organization or a responsible person about the patient with a positive result, who notifies the territorial DKKBTU of the Ministry of Health of the Republic of Kazakhstan within 2 hours; II. PCR testing

• 2. Material for detecting COVID-19 is a sample of discharge from the pharynx and nasopharynx, transtracheal, nasopharyngeal aspirate, nasal wash, sputum.

• 3. Sampling of biomaterial is carried out by a medical worker of a healthcare organization in compliance with the requirements of an anti-epidemic regime.

• 4. PPE is used when collecting material.

• 5. Samples of smears are taken at the location of the tested person (at home, in a medical organization, provisional and quarantine hospitals, at the place of work) using a sterile swab with an artificial applicator. [59]



[60]

Treatment

Compliance with the anti-epidemic regime is recommended in accordance with the PGSP. Patients with mild to moderate illness should avoid being sedentary, dehydrated and active (walking) and drink enough fluids while isolated at home. Relief of fever (non-steroidal anti-inflammatory drugs - paracetamol, ibuprofen, physical methods of cooling).

Patients need to monitor temperature, pulse rate, respiration, blood pressure, oxygen saturation (if there is a pulse oximeter). With an increase in clinical symptoms, the district doctor determines the severity of the condition and further patient management.

Persons without clinical symptoms at the time a positive PCR result is detected within 14 days of observation (duration of the incubation period) may develop a disease, therefore they are subject to medical supervision by primary care at home in accordance with the order of the Ministry of Health of the Republic of Kazakhstan (09.07.2020, 10-1- 0/4897-ext.).

When clinical symptoms appear (fever, cough, shortness of breath, shortness of breath) during the period of medical observation, the local doctor determines the further tactics of managing the patient.

In the absence of manifestation of clinical symptoms within 14 days from the moment of the last contact with a patient with COVID-19, medical supervision is removed.

The management of patients with mild disease depends on the presence of risk factors. Persons without concomitant diseases are recommended acetylsalicylic acid at a dose of 75/150 mg per day. If there are contraindications to the appointment of acetylsalicylic acid, clopidogrel 75 mg per day. Individuals with co-morbid conditions should assess the risk of venous thromboembolism using the Padua scale or the IMPROVE Risk and Bleeding Model for therapeutic patients (Appendix 3). In the presence of risk factors (age over 65, obesity, diabetes mellitus, hypertension, CHF, etc.), patients require careful monitoring, especially from the second week of the disease.

Patients taking oral anticoagulants according to indications (permanent form of atrial fibrillation, history of deep vein thrombosis, etc.) are recommended to continue taking them.

Persons with a mild form of the disease are removed from medical supervision in the absence of elevated body temperature and regression of respiratory symptoms for> 3 days (PCR studies and CT / X-ray diagnostics are not required).

At a high risk of thromboembolic complications, prophylactic oral anticoagulants are recommended on an outpatient basis.

Oral anticoagulants:

Rivaroxaban 10 mg, once a day, within 10 days, OR

Apixaban 2.5 mg, 2 times knocks, within 10 days,OR

Dabigatran etexilate 110 mgx 2 times a day – 10 days

Pathogenetic therapy

In case of mild and moderate forms of the disease, it is strongly recommended to drink plenty of warm water (for the purpose of detoxification, moisturizing the mucous membranes. At high temperatures, loose stools, enteral fluid replacement is necessary (Appendix 1).

Relief of fever (non-steroidal anti-inflammatory drugs - paracetamol, ibuprofen, physical cooling methods).

ACTs are recommended for hospitalized patients with COVID-19, the dose of drugs (prophylactic, intermediate or therapeutic) is selected depending on the risk of thromboembolic complications and the severity of the disease

In severe cases of COVID-19, a cytokine release syndrome (cytokine storm) develops, which poses a threat of the onset and progression of ARDS, multiple organ failure and death. Therefore, it is extremely important to diagnose the cytokine storm at the early stages of its development.

Corticosteroids are recommended in stationary conditions for the treatment of severe immuno-inflammatory syndrome in patients with severe course with the threat of development and manifestation of a cytokine storm to suppress the hyperimmune response. Dexamethasone may be considered for use in patients with severe COVID-19 to reduce mortality.

Etiotropic therapy

Currently, numerous clinical trials are being carried out all over the world (such as RECOVERY, SOLIDARITY, etc.), the final or intermediate results of which make it possible to regularly analyze and revise approaches to empirical treatment of patients with COVID-19 with experimental drugs with supposed etiotropic efficacy (prescription off-label).

In the current situation, due to the lack of evidence base for the treatment of COVID19, the use of etiotropic drugs in patients with COVID-19 is permissible if the potential benefit for him outweighs the risk of their use, and the patients (relatives, guardians, etc.) have previously signed informed consent (Appendix 7).

Etiotropic drugs are prescribed in order to suppress viral replication and reduce viral load, and therefore it is important to start therapy early within the therapeutic window (in the first 72 hours from the onset of clinical manifestations to the development of a widespread process in the lungs). At a later admission of patients, the appointment of etiotropic drugs is also recommended, but their effectiveness may be lower.

Antibiotic therapy for COVID-19: Lung viral disease in COVID-19 is not an indication for starting empiric antibiotic therapy. The appointment of ABT is indicated when secondary bacterial pneumonia is attached

CLINICAL PROTOCOL OF DIAGNOSTICS AND TREATMENT

CORONAVIRUS INFECTION COVID-19 by the Joint Commission on the Quality of Health Services of the Ministry of Health

Of the Republic of Kazakhstan dated July 15, 2020 Minutes No. 107

Prevention

• Stay at least 1 meter away from people, especially if they have a cough, runny nose and fever. When you are indoors, you must maintain additional distance. The more distance you stay, the safer.

• Get in the habit of wearing a mask in crowded places.

The basic rules for wearing masks are presented below:

• Perform hand hygiene before putting on or taking off the mask.

• Put on the mask so that it covers your nose, mouth and chin.

Below you will find information on which type of mask is suitable for different situations, depending on the risk of contracting the virus in your area of residence, location or occupation.

• In case you do not belong to one of the risk groups, wear a cloth mask. This is especially important when it is impossible to maintain a safe distance, in particular in closed and poorly ventilated crowded places.

• Use a medical / surgical mask in the following cases:

o you are over 60 years old;

o you suffer from chronic diseases;

o you notice that you are not feeling well; and / or

o you are caring for an ill family member.

• Face masks are essential personal protective equipment for healthcare professionals caring for patients with suspected COVID-19 or probable or confirmed diagnosis. Carefully sized respirators (such as FFP2, FFP3, N95, N99) must be worn when performing aerosol-generating procedures.

Don't forget about basic hygiene rules

• Regularly clean your hands with alcohol or wash them with soap. This measure will eliminate possible microbial contamination of the hands, including viral ones.

• Whenever possible, do not touch your eyes, nose and mouth. A person touches many surfaces with his hands, so there is a possibility of viral particles getting on

them. Once on the hands, viral particles can enter the eyes, nose or mouth. From these parts of the body, the virus can invade the body and cause disease.
• Cover your mouth or nose with the fold of your elbow or tissue when you cough or sneeze. The used tissue should be immediately thrown into a container with a resealable lid and your hands should be washed. By strictly observing respiratory hygiene, you can protect those around you from diseases caused by viruses such as SARS, influenza and COVID-19.

• Regularly clean and disinfect surfaces, especially those that are frequently touched by people, such as doorknobs, taps, and phone displays. [61]

Conclusion

Influenza and other respiratory viral infections (ARI) annually cause mass outbreaks of diseases that have the character of epidemics. Influenza and acute respiratory viral infections remain virtually uncontrolled diseases due to the variability of the antigenic structure and virulence of circulating viruses. The latest example of such changes is severe acute respiratory syndrome, known as atypical pneumonia (SARS), caused by a Coronavirus belonging to the group of pathogens of acute respiratory viral infections. The damage caused by these infections to the health of the population is enormous. Hundreds of people die every year from the flu or related complications.

The epidemiological role of different viruses is not the same. 20 million victims of the Pandemic Influenza A in 1918, known as the "Spanish flu", will forever remain in the memory of humanity, which until recently was considered the most dangerous influenza A. Over the past 20 years, there have been fundamental changes both in the virus itself and in the anti-epidemic surveillance system. The coronavirus, which has gripped the entire world, seems to be firmly rooted in criticizing not only the medicine, economy, and power of the defense system of states, but also the humanity and responsibility of their residents. The assumption of Chinese scientists that the epidemic can affect 70 percent of the world's population is becoming a reality. On March 11, the World Health Organization declared coronavirus infection a pandemic.

The group of pathogens of acute respiratory viral infections includes about 10 species of viruses belonging to different families, 5 of which are of great epidemic importance. All acute respiratory viral infections are characterized by various complications in the form of bronchitis, sinusitis, pneumonia, these complications pose a serious threat to the health of the population.

Previously, the doctor had various symptomatic remedies at his disposal, which were eliminated without a significant impact on the manifestation of the disease – the virus. The modern approach involves an emphasis on the prevention and stimulation of natural immunity.

Now, unfortunately, there is a significant gap between the methods of diagnosis of respiratory viral infections proposed by modern virology and Molecular Biology and the level of implementation of these capabilities in our practical laboratories. Etiotropic therapy of acute respiratory viral infections also remains an open question, as the arsenal of active drugs against respiratory viruses is currently

limited. According to who, every third person in the world suffers from acute respiratory viral infections every year. Therefore, the need for qualitatively new approaches to the prevention and treatment of acute respiratory viral infections has become obvious, since even highly effective influenza vaccination alone does not guarantee protection from the entire acute respiratory viral infections complex.

1. Questions to control the assimilation of the material

1. Taxonomic position of influenza viruses.
2. The structure of the influenza virus.
3. The reproduction cycle of the influenza virus.
4. Epidemiology and pathogenesis of influenza.
5. The clinical picture of influenza.
6. Laboratory diagnostics of influenza.
7. Principles of influenza treatment.
8. Prevention of influenza.
9. Morphological and cultural properties of adenoviruses.
10. Resistance and epidemiology.
11. Pathogenesis.
12. Clinic and immunity.
13. Diagnostics.
14. Treatment and prevention.
15. Historical background of the coronavirus.
16. Systematics of the coronavirus.
17. Morphological and tinctorial properties of coronavirus.
18. Cultural properties of the coronavirus.
19. Coronavirus resistance.
20. Epidemiology of Coronavirus.
21 Factors of pathogenicity of the causative agent of coronavirus.
22. pathogenesis of coronavirus.
23. Coronavirus infection clinic
24. Immunity in coronavirus infection.
25. Diagnostics.
26. Treatment of coronary infection.
27. Prevention of coronavirus.

Test tasks

1. Influenza viruses belong to the family:

A. Togaviridae

B. Orthomyxoviridae

C. Retroviridae

D. Adenoviridae

E. Flaviviridae

2. The influenza virus contains:

A. DNA
B. RNA
C. RNA-dependent RNA polymerase
D. supercapsid
E. reverse transcriptase

2. The genome of influenza type A virus is represented by:

A. one DNA molecule

B. 8 minus RNA segments

C. 7 minus RNA fragments

D. one plus-RNA molecule

E. 8 plus-RNA fragments

4. The life cycle of the influenza virus occurs:

A. on the membrane of the target cell
B. in the intercellular space
C. in the cytoplasm and cell nucleus
D. in blood serum

E. in the cerebrospinal fluid

5. The influenza virus is characterized by:

A. no supercapsid
B. the presence of a supercapsid shell
C. segmented genome
D. presence of a polymerase complex
E. DNA genome

6. The influenza virus is characterized by:

A. alimentary transmission route
B. airborne transmission
C. source of infection - human
D. source of infection - rodents
E. fecal-oral transmission mechanism

7. For laboratory diagnosis of influenza use:

A. feces
B. urine
C. nasopharyngeal lavage
D. water
E. liquor

8. Cells - targets for the influenza virus are:

A. erythrocytes

B. T-lymphocytes

C. epithelium of the upper respiratory tract
D. B-lymphocytes
E. alveolar macrophages

9. The development of an influenza epidemic leads to:

A. antigenic shift
B. antigenic drift
C. change in protein M1
D. NP protein change
E. violation of RNA synthesis

10. Influenza pandemic development is caused by:

A. antigenic drift
B. antigenic shift
C. change in protein M1

D. NP protein change
E. violation of RNA synthesis

11. In what year were the adenoviruses isolated.

A. 1953

B. 1921

C. 1965

D. 1918

12. Which of the researchers was the first to isolate the adenovirus.

A. W. Rowe et al.

B. Wilson Smith

C. Richard Shoupe

D. Thomas Francis

13. Family of adenoviruses

A. DNA-containing

B. RNA containing

C. DNA and RNA containing

14.Nucleocapsid of adenovirus virion.

A. Sphere

B. Icosahedron

C. Triangle

D. Rhombus

15. Adenovirus is not cultivated

A. Chicken embryos

B. Primary trypsinized cells

C. Transplantable cell cultures

16. Adenovirus is inactivated

A. At pH 5.0-9.0

B. Freezing and lyphilization

C. At t above 56^0C and UV irradiation

D. At t below 500C

17. Source of adenovirus infection

A. Pets - cats, dogs

B. Sick person with acute or latent infection

C. Cows, horses

D. Poultry - chickens, geese.

18. Infection with adenovirus occurs

A. By airborne, contact-household, fecal-oral route.

B. Airborne

C. Contact and household

D. Fecal-oral

19. Incubation period of adenovirus infection

A. 1-2 days

B. 3-4 days

C. 5-14 days

D. 21 days

20.What is the main type of biomaterial for laboratory PCR research in the diagnosis of COVID-19?

1) swab from the nasopharynx and / or oropharynx

2) sputum

3) blood

4) feces and vomit

5) urine

22. How long is the incubation period for coronavirus infection?

1) 3-4 days

2) 7-10 days

3) 5-8 days

23. What is the name of the new coronavirus?

1) SARS-CoV-19

2) MERS-CoV

3) 2019-nCoV

4) SARS-CoV-2

5) SARS-CoV

24. The most characteristic routes of transmission of coronavirus infection are

1) air-dust, food, contact and household

2) transmission, contact, food

3) transplant, sexual, parenteral

4) alimentary, perinatal, blood transfusion

5) contact, airborne, aerosol

25. What is the causative agent of coronavirus infection?

1) Picornoviridae

2) Paramyxoviridae

3) Coronaviridae

4) Reoviridae

5) Adenoviridae

26. Currently, the main source of infection for coronavirus infection COVID-19 is

1) bacteria carrier;

2) a sick person;

3) a sick person, including during the incubation period;

4) convalescence;

5) a sick animal.

Correct answers

1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**
B	B,C,D	B	C	B,C,D	B,C	C	C	B	B
11	**12**	**13**	**14**	**15**	**16**	**17**	**8**	**19**	**20**
A	A	A	B	A	C	A	C	C	A
21	**22**	**23**	**24**	**25**	**26**	**27**	**28**	**29**	**30**
B	A	E	B	A	B	D	E	C	C

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