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HIGHER EDUCATION "NORTH OSSETIAN STATE MEDICAL  
ACADEMY»  
MINISTRY OF HEALTH OF THE RUSSIAN FEDERATION

Department of Infectious diseases

## **METHODOLOGICAL GUID**

### **RABIES**

for students studying in the specialty  
31.05.01 General medicine (specialty)

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Rabies (Rabies, Lyssa, Hydrophobia - hydrophobia-hydrophobia, phobodipsia) is an acute viral disease of warm-blooded animals and humans, characterized by the development of severe progressive polyencephalomyelitis with degeneration of neurons in the brain and spinal cord and absolute (100%) mortality.

The disease has been known since ancient times and is mentioned in the writings of Aristotle (322 BC), Cornelius Celsus (1st century AD), who called this disease hydrophobia, etc. The victory over the disease as a result of its prevention is associated with names Pasteur, Roux and Chamberlain. The first vaccination against rabies was carried out by L. Pasteur on July 6, 1885, to the boy Joseph Meister, bitten by a rabid dog (later, for many years, he served as a doorman at the Paris Pasteur Institute) L. Pasteur achieved outstanding results in many years of rabies research: he developed a vaccine, and already within In 1886, 2,500 lives were saved thanks to rabies vaccinations. Since that time, in various countries, including Russia (in Odessa, 1906), Pasteur stations were organized, where vaccinations against rabies were carried out. In 1882 V.

### ETIOLOGY

The causative agent of rabies virus (Neuroroyetes rabies), belongs to the family of rhabdoviruses (Rhabdoviridae), genus Lyssavirus, contains RNA, has a bullet shape with one flat end and one rounded end. The sizes of the virion are 75-180nm. The neurotropene virus exists in two variants: "street" ("wild"), which circulates in natural conditions among animals, is highly pathogenic for mammals, causes disease and "fixed" (virus fixes), received by Pastera after repeated passages in laboratory animals during adaptation of the "street" virus to the rabbit body under altered conditions of infection, is used to obtain vaccines, is non-pathogenic, does not affect peripheral nerves. The antigens of the "street" and "fixed" viruses are identical. The viral nature of the rabies causative agent was proved by Remling in 1903, having carried out the experience of filtering infectious material through bacterial filters (V.I. Pokrovsky, 1986). The rabies virus is not resistant in the external environment. Boiling kills the virus within 2 minutes, it quickly dies under the influence of various disinfectants (2-3% solution of chloramine, lysol, 0.1% solution of mercuric chloride). In animal carcasses, the virus can persist for up to 3-4 months. The rabies virus

### INTRODUCTION

has antigenic, immunogenic and hemagglutinating properties. The reproduction of the virus is accompanied by the formation of specific inclusions-Babesha-Negri bodies, 0.5-2.5 nm in size, located in the cytoplasm of neurons, have a rounded, oval, less often spindle-shaped shape, are stained with sour dyes in a ruby color. Boiling kills the virus within 2 minutes, it quickly dies under the influence of various disinfectants (2-3% solution of chloramine, lysol, 0.1% solution of mercuric chloride). In animal carcasses, the virus can persist for up to 3-4 months. The rabies virus has antigenic, immunogenic and hemagglutinating properties. The reproduction of the virus is accompanied by the formation of specific inclusions-Babesha-Negri bodies, 0.5-2.5 nm in size, located in the cytoplasm of neurons, have a round, oval, less often spindle-shaped shape, stained with sour dyes in a ruby color.

### **EPIDEMIOLOGY**

The disease is widespread everywhere, with the exception of island states (England, the Caribbean, etc.). In recent years, in Russia and in some of its territories, including in the Republic of Dagestan, there has been a worsening of the epidemic and epizootic situation of rabies (N.D. Yushchuk et al., 1999; G.G. Onischenko, 2000). Rabies is a typical contact zoonosis. The main reservoirs and sources of rabies are carnivorous wild animals from the canine family (foxes, raccoon dogs, wolves, jackals), mustelids (skunks, martens, badgers, weasels, ferrets, ermines), felines (wild cat, lynx, etc.), civet (genetas, civets, mongooses) and bats (vampires, insectivorous and carnivorous bats), as well as domestic animals - dogs, cats, secreting viruses with saliva in the last 7-10 days of the incubation period and throughout the disease. Transmission of infection from animals to humans occurs through the bite of a rabid animal, and it is also

possible for the pathogen to penetrate through damaged skin (for example, scratches) and mucous membranes when sick animals salivate. In the saliva of animals, the virus appears several days before the onset of clinical manifestations, which increases the risk of developing rabies after being bitten by up to 40%. After the virus enters the central nervous system of a sick animal, the risk of infection through a bite is reduced to 10%. The virus is usually not transmitted from person to person. The most dangerous bites are in the head, neck and hands. The susceptibility to rabies is universal. There are two types of the disease - forest and urban rabies. Transmission of infection from animals to humans occurs through the bite of a rabid animal, and it is also possible for the pathogen to penetrate through damaged skin (for example, scratches) and mucous membranes when sick animals salivate. In the saliva of animals, the virus appears several days before the onset of clinical manifestations, which increases the risk of developing rabies after being bitten by up to 40%. After the virus enters the central nervous system of a sick animal, the risk of infection through a bite is reduced to 10%. The virus is usually not transmitted from person to person. The most dangerous bites are in the head, neck and hands. The susceptibility to rabies is universal. There are two types of the disease - forest and urban rabies. scratches) and mucous membranes when salivated by sick animals. In the saliva of animals, the virus appears several days before the onset of clinical manifestations, which increases the risk of developing rabies after being bitten by up to 40%. After the virus enters the central nervous system of a sick animal, the risk of infection through a bite is reduced to 10%. The virus is usually not transmitted from person to person. The most dangerous bites are in the

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The main reservoir of wild (forest) rabies are wild animals specific, for example, skunks for the USA, Russia and North America-foxes, for the Caribbean and South America-vampire bats. For urban rabies, sick dogs (up to 90% of all cases) and cats represent the greatest epidemic danger. In Nigeria, the latter transmit to humans the Mokola virus, which is close to rabies, which causes neurological diseases (paralysis) with a fatal outcome.

### **PATHOGENESIS**

The virus multiplies in muscle and connective tissue, where it persists for weeks or months. Then the virus migrates along the axons of peripheral nerves in the basal ganglion and central nervous system. From the site of introduction, the rabies virus spreads along the nerve trunks (perineural spaces), reaching the brain and spinal cord. Reproduction of the virus occurs in the neurons of the medulla oblongata, the hippocampus, in the nodes of the base of the brain and the lumbar spinal cord. The centrifugal spread of the virus from the central nervous system into the salivary glands promotes its release into the external environment with saliva.

Reproduction of the virus in the central nervous system results in degenerative changes in neurons, edema, hemorrhages, and lymphocytic infiltrates around the affected areas. In the cytoplasm of the cells of the

affected brain, characteristic eosinophilic inclusions are formed - the Babesha-Negri bodies.

All this leads in the early period of the disease to an increase in reflex excitability, and in the late period - to the development of paralysis and death of the patient.

Paresis and paralysis in patients with rabies can be explained by the corresponding lesions of the spinal cord and brain stem. Some authors (N.M. Krol, 1936) explain rabies paroxysms in the light of Ukhtomsky's doctrine of the dominant, according to which the increased excitability of the higher vegetative centers of the medulla oblongata hypothalamus and subcortical formations creates a dominant that absorbs all other irritations. Therefore, any irritation is followed by a response in the form of a paroxysm of rabies (V.I. Pokrovsky, 1986).

### **CLINIC**

The incubation period of the disease lasts from 10 days to 1 year (usually 1-3 months), it can be reduced to 6 days, depending on the remoteness of the place of penetration of the virus from the brain. According to V.I. Pokrovsky, 1986 the incubation period shorter than 10 days should be classified as casuistic, and the incubation period from 2 to 10 years described by a number of authors is unlikely. A.I. Savateev (1927) observed the following duration of the incubation period: from 12 to 99 days - 94%, from 100 to 200 days - 10.4%, from 200 days to 1 year - 3.7%, more than 1 year - 1.1%. The variability of the incubation period is associated with various factors: the localization of the bite (the shortest is for bites in the head, hands, the longest for bites in the feet), the age of the bitten (shorter in children than in adults), the type of the bitten animal, reactivity macro-organism, the size and depth of the wound, i.e. the severity of tissue damage, the dose of the pathogen that got into the wound.

During the course of the disease, there are 3 stages: prodrome (depression), excitement, paralysis.

*In the prodrome, the duration of which is 1-3 days, irritability, insomnia, sensory disturbances (paresthesia - burning sensation, itching), pulling and aching pains in the area of the healed wound and along the nerve trunks nearest to it.*

The first signs of an incipient disease are almost always found at the site of the bite. General malaise, headache, dyspeptic symptoms occur, appetite decreases, hypersensitivity to auditory and visual stimuli appears, the temperature becomes subfebrile.

The patient is depressed, does not sleep well, sleep is accompanied by nightmares, he experiences unreasonable fear, anxiety, melancholy.

*Stage of excitement. Apathy and depression are replaced by anxiety, accompanied by increased breathing and pulse. Paroxysms of hydrophobia appear. When you try to drink, and soon at the sight of water, its gurgling, splashing, verbal mention of it, there is a feeling of horror and painful spasms of the muscles of the pharynx and larynx. Paroxysms can be triggered by air movement, bright light, loud sound (hydro-, aero-, photo- and acoustic phobia). The attack is characterized by a sudden tremor of the whole body, arms are stretched forward, the patient throws back his head and torso with a cry, his hands tremble, pushes a vessel of water away. Painful convulsions distort the face, which becomes cyanotic and expresses horror, the pupils dilate, the gaze rushes to one point, the neck stretches. Inspiratory shortness of breath develops, The patient breathes in air with a whistle, begs for help, vomiting is sometimes observed. The attacks last for a few seconds. Gradually, excitement grows, auditory and visual hallucinations of a threatening nature are possible, bouts of violence with aggressive actions, they scratch and bite themselves and others, spit, scream and rush in fierce despair, break furniture, showing inhuman ("frenzied") strength. Attacks are accompanied by clouding of consciousness with the development of auditory and visual hallucinations of a frightening nature. There is increased sweating, profuse painful salivation (sialorrhea), the patient cannot swallow saliva and constantly spits it out or it runs down the chin. The skin is covered with cold clammy sweat, the limbs are cold. The body temperature is subfebrile, its level increases in parallel with the course of the disease, the pulse is speeded up.*

The duration of the arousal stage is 2-3 days, rarely up to 6 days. If during the period of an attack the patient does not die from cardiac or respiratory arrest, the disease passes into the paralytic stage 1-3 days before death (N.D. Yushchuk et al, 1999; E.P. Shuvalova, 2001).

*The paralytic stage is manifested by the cessation of attacks of hydro- and aerophobia, fear and anxious-melancholy mood disappear, there*

*is an opportunity to eat and drink, there is a hope for recovery ("ominous calm"). Along with this, lethargy, apathy, salivation and paralysis of the muscles of the limbs, tongue, face, and cranial nerves develop. Death occurs from paralysis of the heart or respiratory center.*

The total duration of the disease is 3-7 days, in rare cases 2 weeks or more.

Sometimes a disease without prodromal symptoms begins immediately with arousal or with the onset of paralysis.

Among other variants of the disease, there is a tabloid form with severe symptoms of damage to the medulla oblongata, paralytic ("silent rabies", the first two stages are absent, and the disease often develops as Landry's ascending paralysis) and cerebellar with severe cerebellar disorders. Death occurs with an increase in bulbar paralysis.

For illustration, we present cases of rabies in the Republic of Dagestan. Thus, in August 1997, in the Kizlyar region, N. was bitten by a wolf, who asked for help at the first-aid post of a military unit located in the same region. The victim was provided with first aid: they performed surgical treatment of wounds on the face, back of the head and right hand, and emergency prevention of tetanus. Subsequently, the wounds healed. And after 1.5 months, in October of the same year, the man developed a typical clinical picture of rabies. The patient was admitted to the Kizlyar TMO, where he died a few days later. As can be seen from the above case, the onset of the disease is associated with untimely seeking medical help from a wolf bite victim, and at the time the patient was identified, there was no supply of rabies vaccine and immunoglobulin in the DM. In July 1999 K., 52 years old, in Derbent was bitten by the hand by a stray dog. The attack of the dog was unprovoked, sudden, and, having bitten, the animal no longer opened its jaws; only after killing the dogs were able to free the hand. On the same day, K. was taken to the district hospital, where he received first aid: wound treatment and emergency prevention of tetanus. After a while, the wound on the arm healed.

*On September 3 of the same year, more than 2 months after the bite, K. developed general weakness and malaise. In the following days, anxiety, anxiety began to grow, a feeling of a painful lump appeared in my throat. Because of the sharp and painful spasms of the swallowing and respiratory muscles, drinking water became impossible, and hydrophobia devel-*



oped. Soon all other signs of rabies appeared: hypersalivation, psychomotor agitation with short-term hallucinations, fever, etc. The patient was admitted to the RCCH on October 4, that is, on the 5th day of illness in a serious condition. On the 2nd day of hospitalization, the paralytic stage began: progressive paralysis of the ascending type developed. On the 2nd day of inpatient treatment and on the 7th day from the onset of the disease, death occurred from respiratory paralysis and a drop in cardiac activity.

An autopsy was performed on the corpse. As a result of the autopsy, the clinical diagnosis was fully confirmed - a histological picture of viral encephalitis and specific inclusions in neurons - Babesh-Negri's little bodies - were found. The main diagnosis: rabies (viral encephalitis with a primary lesion of the brain stem). Complications - bulbar syndrome, respiratory paralysis.

As in the previous case, in this example, the same mistakes were made, indicating the lack of alertness on the part of the medical workers of the medical network regarding this infection, about the low health education work among the population on the problem of rabies and the late seeking of antirabies help.

The next incident took place on September 25, 1999 in the Derbent region. A dog unfamiliar to the local residents appeared in the village of Michurin in this area. The behavior of the dog was strange: like a predator, it sneaked up on geese and chickens, and when it was driven away, it showed aggressiveness. In the courtyard of a house, she bit a little boy. On the street, she bit a teenager and a woman, and the dog bit the teenager in the face.

After 2 weeks, the teenager bitten in the face developed discomfort and sore throat, as well as pains in the upper abdomen, headache, fever, became restless, slept badly at night. Soon the characteristic symptoms of rabies appeared - hypersalivation, hydrophobia, hallucinations. On October 13, the patient was taken to the regional hospital, and on October 15, he was taken to the RCIBg. Makhachkala diagnosed with rabies? On admission he was agitated, at times hallucinations, talkativeness, insomnia, anxiety were noted. In the following days, the patient had thirst, growing weakness, could hardly move around the ward. Shortness of breath, tachycardia, fever, sweating were expressed. Later, paralysis of the lower ex-

trémities developed according to the type of ascending paralysis of Guillain-Barre-Landry.

The rabies vaccination of the rest of the bitten, carried out according to unconditional indications, allowed them to avoid the development of the disease. A survey of those bitten in the village of Michurin showed that after the attack, the dogs underwent primary surgical treatment of wounds and emergency prophylaxis of tetanus, and the rabies vaccine was not administered due to its absence in the area. The sick teenager received the same help.

In February 2000, another case of rabies was reported in Derbent. A 13-year-old boy fell ill. As it turned out, 5 months ago (in October 1999) he was bitten by a dog. The victim was taken to hospital, where the wound on his left forearm was treated. As for the dog, it was shot by the owner, as it became very aggressive, rushed at people and even bitten its puppies. 5 months after the bite, the boy began to complain of general weakness, malaise, he had a fever. I received antipyretics at home, but there was no improvement. On the 3rd day of illness, the condition worsened even more, the boy became restless, episodes of inappropriate behavior appeared. On the same day, hydrophobia was noted: while drinking water, a spasm of the throat arose, and the patient with fear removed the glass. He was taken to the Derbent hospital on the 4th day of illness in a state of psychomotor agitation, with hallucinations and muscle cramps in the face and neck. On the same day, the patient was taken to Makhachkala, to the intensive care unit of the Republican infectious diseases hospital. The boy's condition at admission is extremely difficult, he complained of discomfort in his chest, fear. I rushed about the ward, periodically from my mouth, saliva was coming out paroxysmal in large quantities. After the introduction of sedatives, the patient calmed down for a short time, feeding and drinking it was done through a tube. complained of discomfort in the chest, fear. I rushed about the ward, periodically from my mouth, saliva was coming out in large quantities. After the introduction of sedatives, the patient calmed down for a short time, feeding and drinking it was done through a tube. complained of discomfort in the chest, fear. I rushed about the ward, periodically from my mouth, saliva was coming out paroxysmal in large quantities. After the introduction of sedatives, the patient calmed down for a short time, feeding and drinking it was carried out through a tube.

*Infusion therapy was carried out. Nevertheless, the disease progressed steadily and on the 10th day of illness the boy died. No autopsy was performed.*

### **DIAGNOSTICS**

The diagnosis of rabies is established by comparing the clinical picture of the disease and epidemiological data. Diagnosis of rabies, with the classic version of the course of the disease, is not difficult and is important: 1 carefully collected epid. anamnesis - an indication of a bite or salivation by an animal that died or disappeared, information about the epizootic situation, the type and behavior of the bitten animal, the duration of the incubation period; 2 examination of the patient, while it is necessary to pay attention to the presence of scars from former bites, the condition of the pupils, salivation, sweating, a change in the rhythm of breathing (abruptness, with a deep breath); 3 the appearance of symptoms of mental disorders - sad and depressed mood, mental stress, sleep disorder with frightening dreams. In atypical and erased clinical variants of the course of the disease, it is necessary to differentiate from the following diseases: tetanus, alcoholic delirium ("delirium tremens"), poisoning with atropine, strychnine, hysteria, bulbar forms of rabies should be differentiated from botulism, lethargic encephalitis, poliomyelitis, and paralytic forms from poliomyelitis and infectious polyneuritis. Tetanus is characterized by tonic muscle spasm, against the background of which, under the influence of various stimuli, attacks of tetanic convulsions, trismus and opisthotonus occur. After an attack, muscle tone remains elevated. The muscles of the hands and feet are not involved in the seizure. Consciousness is preserved, there are no delusional statements and hallucinations. The main difference between false rabies and true rabies is the absence of autonomic disorders - mydriasis, sweating, tachycardia, etc. and the dynamics of clinical manifestations. As a rule, there is no aerophobia. In a state of anesthesia, all clinical symptoms disappear.

Virological, biological and serological methods are used to isolate and identify the pathogen. Material for research saliva, blood, sectional material - brain tissue and submandibular salivary glands.

Among the in vivo methods of laboratory diagnostics of rabies: examination of corneal prints, biopsies of the skin, brain using MFA, isola-

tion of the virus from saliva, lacrimal and cerebrospinal fluid by intracerebral infection of newborn mice and rabbits.

In addition, the diagnosis is confirmed by the detection by microscopy of stained sections or imprints in the cells of the cerebral cortex, Ammon's horn and cerebellum of specific inclusions - Babesh-Negri eosinophilic bodies, 5-10 microns in size during histological examination of the brain of a person or animal who died from rabies and the detection of antigens virus in the brain tissue and other organs with the help of RIF or RNIF. And antibodies to the virus in vaccinated individuals are detected in RSK, RN, RIF, etc.

### **TREATMENT**

A patient with clinical manifestations of rabies is incurable. Various drugs, serums and resuscitation methods are ineffective. Primary wound treatment and, if possible, early active and passive immunization are of particular importance. It is necessary to place the patient in a separate ward and provide a therapeutic and protective regime with maximum isolation of the patient from external stimuli, parenteral nutrition and rehydration - the introduction of saline solutions, plasma substitutes, glucose solution, vitamins, antirabies gammaglobulin is used in combination with a complex of resuscitation measures. To relieve convulsive syndrome, aminazine, droperidol, chloral hydrate and other methods are prescribed. In recent years, attempts have been made to treat with antiviral and immunocorrective drugs in combination with cerebral hypothermia,

### **PREVENTION**

Since the treatment of rabies is ineffective, the prevention of the disease in animals is of great importance, including a set of measures to combat epizootics of urban and natural type rabies, aimed at preventing vagrancy of dogs and cats with their obligatory registration, preventive immunization of domestic and farm animals, and combating natural foci of rabies, sanitary and veterinary propaganda, as well as maintaining the population of animals that are a reservoir of rabies at a certain level (track the number of animals and destroy sick ones, add bait with a vaccine to the tanks, apply strict quarantine measures when importing animals). Compulsory vaccine prophylaxis should be carried out in high-risk groups - trap-

pers, veterinarians, etc. In all cases of bites or licks by rabid or unknown animals, it is recommended: a thorough initial treatment of the wound with washing it with soapy water, then treatment with hydrogen peroxide, alcohol or tincture of iodine. Surgical excision of the edges of the wound with suturing is contraindicated, as it leads to additional trauma and shortening of incubation. After providing first aid, the patient is immediately sent to the Pasteur station. In Makhachkala, this is the Republican Center for Antirabies Aid under the Republican Orthopedic and Traumatology Center. Specific immunoprophylaxis of rabies is carried out with rabies vaccine and rabies immunoglobulin. Before carrying out, you should pay attention to the nature of the lesion (bite or drooling), the type of animal suspicious of rabies, the circumstances of the attack (right-sided or not), the presence of previous rabies vaccination (at least in humans), other cases of rabies in the region. If the animal is rabid or suspected of being rabid, rabies immunoglobulin should be injected under the skin around the wound. Postpone the application of the bandage for a while, but if the bandage is necessary, use the immunoglobulin topically. Then they start anti-rabies vaccinations, which are methods of emergency prevention of the disease. There are anti-rabies vaccinations for unconditional and conditional indications. Unconditional indications are the bites of rabid animals, as well as animals that have remained unknown. Vaccinations for conditional indications are carried out when bitten by animals without signs of rabies and when these animals are quarantined for 10 days. Antibodies after the introduction of the vaccine appear only after 12-14 days, therefore, with unconditional indications, bites of a dangerous localization (head, neck, fingers), prevention begins with the introduction of anti-rabies immunoglobulin. Detailed information on the doses, duration of vaccination, depending on its type, animal behavior, localization of bites are set out in the instructions of the Ministry of Health of the Russian Federation. Currently, for active immunization, cultural vaccines made from an attenuated virus obtained from various cell lines are used. Such vaccines, in contrast to vaccines made from attenuated or killed virus grown on nerve cells Detailed information about the doses, duration of vaccination, depending on its type, animal behavior, localization of bites are set out in the instructions of the Ministry of Health of the Russian Federation. Currently, for active immunization, cultural vaccines made from an attenuated virus, obtained on lines of various

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## **ANNEXES**

### **ORDER**

**Ministry of Health of the Russian Federation from 07.10. "7 No. 297**

### **ON IMPROVEMENT OF MEASURES FOR THE PREVENTION OF THE DISEASE PEOPLE BY RABIES**

In connection with the aggravation of the epidemic situation of rabies in the territory of the Russian Federation in recent years, the threat of the spread of this infection among the population has significantly increased.

The number of cases of rabies among animals has almost doubled in the last two years, the number of disadvantaged settlements has reached



1240, which is 44.5% more than in 1995. The situation is aggravated by an increase in the number of neglected animals, widespread violation of the rules for keeping domestic animals, and unsatisfactory implementation of hunting and economic measures to regulate the number of wild animals in natural conditions. The most persistent natural foci of rabies persist in the Central, Central Black Earth, North Caucasian, Volga, Ural, Far Eastern regions of the country.

In the same areas, cases of people with this infection are recorded. The number of lindens damaged by animals in the 90s has more than doubled compared to the 80s. In 1996, 439 thousand people applied for medical help, of which 34.5% were children under the age of 14. Specific anti-rabies treatment was prescribed to 47% of the victims. The number of people who self-stopped the course of anti-rabies vaccinations increased in 1996 to 11.4% against 7% in 1990.

In the Russian Federation, from 5 to 20 cases of rabies among humans are registered annually. In 1996, 8 people died from rabies, for 8 months of 1997 - 8 people (in the Republic of Bashkortostan, Krasnodar Territory, Astrakhan, Moscow, Kursk, Orel, Samara regions). At the same time, out of 16 deaths from rabies in 1996 and 1997, in 10 cases, the occurrence of diseases was associated with the untimely appeal of victims of animal bites for medical help, in two cases - with their refusal from the proposed vaccination, in two cases of the disease arose through the fault of medical workers who, if indicated, did not prescribe a course of vaccinations.

The introduction of concentrated purified cultural rabies vaccine (COCAV) into public health practice in 1993 made it possible to reduce the scheme of a full course of vaccination to 6 injections and to reduce a single vaccination dose to 1 ml. However, despite the recommendations of the Russian Ministry of Health "On the expansion of the use of cultured purified concentrated rabies vaccine (COCAV) with rabies immunoglobulin", in a number of territories, health authorities and institutions are not taking measures to introduce this highly effective vaccine.

There is no production of antirabies immunoglobulin in the country, which is necessary for combined use with a vaccine in case of severe injuries and injuries of dangerous localization received from animals.

The quality of rabies care for the population is negatively affected by the lack of territorial advisory and methodological centers for the provision of rabies care, insufficient training of traumatologists and surgeons who directly provide rabies care, and lack of alertness regarding this infection, especially among medical workers in rural areas. The level of awareness-raising work among the population on the rabies problem remains low. All this leads to the fact that a significant number of people who have suffered from animals, not attaching importance to the danger of this infection, do not seek medical help on time or arbitrarily stop the prescribed course of specific anti-rabies treatment.

The Sanitary-Anti-Epidemic Commission of the Government of the Russian Federation, by its decision (Protocol of June 22, 97 No. Ts), drew the attention of health authorities and institutions and the State Sanitary and Epidemiological Service to the need to improve the provision of anti-rabies care to the population.

In order to improve the quality of the provision of anti-rabies care and improve measures for the prevention of human disease with rabies

**I order:**

1. To the heads of public health authorities of the constituent entities of the Russian Federation:

1.1. To organize, by January 1, 1998, anti-rabies care centers on the basis of one of the medical and prophylactic institutions, which has a trauma center or a trauma department (Appendix No. 1).

1.2. To hold in the IV quarter of 1997, and thereafter annually, seminars for medical workers on anti-rabies care for the population and the prevention of rabies.

1.3. Ensure that copies of the case histories of each rabies case are submitted to the Department of the State Sanitary and Epidemiological Supervision of the Ministry of Health of Russia.

2. Chief state sanitary doctors for the constituent entities of the Russian Federation:

2.1. Together with the chief state veterinarians in the constituent entities of the Russian Federation, introduce, by January 1, 1998, plans for urgent measures to combat rabies in the executive authorities.

2.2. To carry out, together with the center for rabies care, an analysis of the appealability, causes and circumstances of animal bites in humans to prepare proposals for strengthening preventive measures.

3. Heads of health management bodies of constituent entities of the Russian Federation, Chief state sanitary doctors for constituent entities of the Russian Federation:

3.1. Ensure the work of subordinate institutions in accordance with the instruction "On the procedure for the operation of medical and preventive institutions and centers of the State Sanitary and Epidemiological Surveillance for the prevention of rabies in people" (Appendix No. 2).

3.2. To organize, from January 1, 1998, mandatory prophylactic immunization against rabies for persons whose professional activities are associated with the risk of contracting the rabies virus.

3.3. Increase the use of concentrated purified culture rabies vaccine (COCAV) and reduce the use of cultured rabies vaccine.

3.4. Exercise strict control over the availability of anti-rabies drugs and the conditions of their storage in medical institutions.

3.5. To intensify information and explanatory work among the population, using the mass media and visual agitation.

4. The management of the organization of medical care for the population to provide the necessary assistance to the healthcare authorities of the constituent entities of the Russian Federation in organizing the creation of anti-rabies care centers and training personnel.

5. The Administration for the Provision of Medicines and Medical Equipment shall submit, by December 1, 1997, proposals on the organization in 1998 of industrial production in the Russian Federation of anti-rabies immunoglobulins.

6. The Department of State Sanitary and Epidemiological Supervision shall prepare by November 15, 1997 a letter to the heads of the executive authorities of the constituent entities of the Russian Federation on the need to regulate the number of wild animals, take effective measures to reduce the number of neglected animals, observe the rules for keeping pets

and organize special areas for their walking, and build cremation ovens for the disposal of the corpses of neglected animals.

7. The order of the Ministry of Health of the USSR of 05.06.75 No. 540 "On the prevention of human diseases with rabies" shall be considered not valid on the territory of the Russian Federation.

8. Control over the implementation of this order shall be entrusted to the First Deputy Minister of Health of the Russian Federation Onishchenko GG.

### **INSTRUCTION \***

#### **ON THE APPLICATION OF ANTIRABIC CULTURAL PURIFIED CONCENTRATED INACTIVATED DRY AND ANTIRABIC IMMUNOGLOBULIN VACCINE**

The vaccine is a culture of the production strain of the fixed rabies virus Vnukovo-32, passage 3038, grown on a primary culture of Syrian hamster kidney cells, concentrated and purified by ultrafiltration or ultracentrifugation methods, inactivated by ultraviolet rays and formalin. Available in freeze-dried form. Stabilizers - gelatose, sucrose. It is hygroscopic, it is a porous white mass, after dissolution of the mass - a slightly opalescent colorless liquid.

The vaccine induces the development of immunity against rabies. One dose (1.0 ml) contains at least 2.5 International Units (ME)

**Appointment. Medical and preventive and preventive immunization of people.**

**Appointment. Medical and preventive and preventive immunization of people.**

**Mode of application. The contents of the ampoule with the vaccine are dissolved in 1.0 ml of water for injection. The dissolved vaccine is injected slowly intramuscularly into the deltoid muscle. Children under 5 years old - in the thigh muscles (upper part of the anterolateral surface). The gluteal vaccine should never be injected. The drug is not suitable for use in ampoules with impaired integrity, labeling, as well as with a change in color and transparency, with an expired shelf life or improper storage. The opening of the ampoules and**

the vaccination procedure are carried out with strict adherence to the rules of asepsis.

**Dissolved vaccine should not be stored for more than 5 minutes.**

The vaccinated person must be under medical supervision for at least 30 minutes. Vaccination sites should be equipped with anti-shock therapy. After the course of immunization, a certificate is issued indicating the type and series of the drug, the course of vaccinations, post-vaccination reactions.

Rabies care consists of topical wound care, rabies vaccine, or the simultaneous administration of rabies immunoglobulin (RIG) and vaccine.

#### **Local wound treatment.**

Local wound care is extremely important and should be done immediately or as early as possible after a bite or injury; the wound surface is washed abundantly with soap and water (or detergent), and the edges of the wound are treated with 70 ° alcohol or 5% iodine tincture. If there are indications for the use of AIH, it is used immediately before suturing according to the AIH dose section of this instruction.

Suturing the wound should be avoided whenever possible. Suturing is indicated in exceptional cases:

- for extensive wounds - several guiding sutures after preliminary treatment of the wound;
- for cosmetic reasons, the imposition of skin sutures on wounds (faces);

- suturing of bleeding vessels in order to stop external bleeding. After local treatment of the wound, medical and prophylactic immunization is immediately started.

After local treatment of the wound, medical and prophylactic immunization is immediately started.

<b>Primary immunization</b>	<b>Three injections on days 0, 7 and 30 "1 ml each</b>
<b>First vaccination after 1 year</b>	<b>One 1.0 ml injection</b>
<b>The next revaccination every 3 years</b>	<b>One 1.0 ml injection</b>

#### **Treatment and prophylactic immunization**

**Indications.** Contact and bites of people by rabid, suspicious rabies or unknown animals.

**Contraindications.** Absent

Treatment and prophylactic immunization scheme. A detailed treatment and prophylactic immunization scheme and notes to the scheme are presented at the end of the instructions.

If, according to these instructions (point 3, severe injuries), a combined treatment with rabies vaccine and rabies immunoglobulin (RIG) is carried out, then both drugs are administered simultaneously.

**Rabies immunoglobulin (RIG).** Rabies immunoglobulin is given as early as possible after exposure to a rabid, suspected rabid, or unknown animal in accordance with the Vaccination Schedule (see below).

**AIH dose.** Heterologous (equine) rabies immunoglobulin is prescribed at a dose of 40 IU per 1 kg of body weight. Homologous (human) rabies immunoglobulin is prescribed at a dose of 20 IU per 1 kg of body weight.

As much of the recommended dose of AIH as possible should be administered by irrigating the wound and infiltrating the tissue around it. If the anatomical location of the lesion (fingertips, etc.) does not allow the entire recommended dose of AIH to be injected into the tissue around the wound, then the remnants of AIH are injected intramuscularly. The localization of AIH administration should be different from the site of vaccine inoculation (muscles of the buttocks, upper part of the scapula).

Before the introduction of heterologous antirabies immunoglobulin, it is necessary to check the patient's individual sensitivity to horse protein (see "Instructions for the use of antirabies immunoglobulin from liquid horse serum").

#### **Preventive immunization**

**Indications.** For prophylactic purposes, persons whose work is associated with the risk of infection are immunized: laboratory workers working with the street rabies virus, veterinarians, hunters, foresters, dog catchers, slaughterhouse workers, taxidermists.

### **Contraindications for prophylactic immunization**

1. Acute infectious and non-infectious diseases, chronic diseases in the stage of exacerbation or decompensation - vaccinations are carried out no earlier than one month after recovery (remission).
2. Systemic allergic reactions to previous administration of this drug (generalized rash, Quincke's edema, etc.).
3. Allergic reactions to antibiotics of the aminoglycoside group (monomycin, kanamycin, etc.)
4. Pregnancy.

**Immunization of human donors in the production of antirabies immunoglobulin is carried out in accordance with this instruction, 1.0 ml intramuscularly on days 0, 3, 7, 14, 30 and 90.**

### **Reaction to the introduction of antirabies drugs**

1. The administration of the vaccine can be accompanied by a local or general reaction. The local reaction is characterized by slight swelling, redness, itching, and an increase in regional lymph nodes. The general reaction can manifest itself in the form of malaise, headache, weakness, fever. Symptomatic therapy, the use of hyposensitizing and antihistamines are recommended. In rare cases, neurological symptoms may be reported. In this case, the victim should be urgently hospitalized.

2. After the administration of rabies immunoglobulin from horse serum, complications can occur: anaphylactic shock, local allergic reaction occurring 1-2 days after administration, serum sickness, which occurs most often on 6-8 days. In the case of an anaphylactic reaction, it is injected into the subcutaneous tissue, depending on the patient's age, from 0.3 to 1.0 ml of epinephrine (1: 1000) or 0.2-1.0 ml of ephedrine (5%). For the treatment of patients with serum sickness, it is recommended to administer diphenhydramine at 0.05-0.1 ml

inside 3-4 times a day, calcium chloride intravenously or inside, corticosteroid drugs (prednisone, prednisone, cortisone) and hospitalization if indicated.

**Release form Vaccine release kgg in ampoules of 1.0 ml (1 dose). Solvent: water for injection, 1.0 ml. The package contains 10 ampoules, including 5 ampoules with a solvent. Immunoglobulin from horse serum is produced in ampoules of 5.0 or 10.0 ml; diluted 1: 100 -**

**1.0 ml in an ampoule. Produced in a set: 1 ampoule of immunoglobulin and 1 ampoule of immunoglobulin. Divorced 1: 100. The package contains 5 sets.**

**Shelf life. Storage and transportation conditions. The shelf life of the vaccine is 1.5 years, the shelf life of the immunoglobulin is indicated on the package and in the attached instructions. The vaccine is stored in a dry, dark place at a temperature (5-3) °C.**

Transportation by all types of covered transport at a temperature (5-3) °C.

**Complaints Submission Rules. In case of complications or a person's illness with hydrophobia after a full course of vaccinations or during its implementation, you should immediately report to the local health department, to the State Research Institute for Standardization and Control of Medical Biological Products. L.A. Tarasevich (121001, Moscow, Sivtsev-Vrazhek, 41, tel. 241-39-22) and to the organization that produced the vaccine or immunoglobulin. Delay the use of a batch of vaccine and rabies immunoglobulin. Samples should be sent to GISK im. L.A. Tarasevich.**

In the event of the death of the vaccinated person, it is imperative to conduct a postmortem autopsy and laboratory diagnostic study. For this, pieces of the brain (Ammon horn, brain stem, cerebellum, cerebral cortex) of a deceased person, extracted in compliance with the rules of asepsis, are placed in a sterile, hermetically sealed vessel filled with a 50% aqueous solution of glycerin, cooled to minus 20 °C and then in containers with ice are urgently sent to the appropriate diagnostic laboratory.

### **Note to the diagram**

1. Local wound treatment is extremely important, and it must be carried out immediately or as early as possible after the bite: the wounds are washed abundantly with soap and water (or detergent), then treated with 70 ° alcohol or 5% iodine tincture.
2. Doses and immunization schedules are the same for children and adults. The course of treatment will be prescribed regardless of the length of time the victim turns for help, even several months after contact with a patient suspected of rabies or an unknown animal.
3. Observation for 10 days is established only for dogs and cats.

4. For persons who have previously received a full course of therapeutic and prophylactic or prophylactic vaccinations, from the end of which no more than 1 year has passed, three injections of the vaccine are prescribed, 1.0 ml per 0; 3 and 7 days, if 1 year or more has passed, or an incomplete course of immunization has been carried out, then - 1.0 ml for 0, 3, 7, 14, 30 and 90 days. According to the indications, the combined use of rabies immunoglobulin and vaccine.

5. Homologous rabies immunoglobulin is prescribed at a dose of 20 IU per 1 kg of body weight and is used according to the same scheme as heterologous immunoglobulin, which is administered at a dose of 40 IU per 1 kg of body weight.

6. Corticosteroids and immunosuppressants can lead to vaccine failure. Therefore, in cases of vaccination while taking corticosteroids and immunosuppressants, the determination of the level of antibodies is mandatory. In the absence of antibodies, an additional course of treatment is carried out.

7. The vaccinated person should know: he is prohibited from drinking any alcohol during the entire course of vaccinations and 6 months after its completion. Overwork, hypothermia, overheating should be avoided.

Cat egor y rria dam age	Animal data	Recommended treatment

	The nature of the contact	At the moment of the bite	3 for 10 days of observation	
denia			niya	
1	2	3	.4	five
1	No damage or indirect contact. Lulling intact	Healthy, sick baby		Not assigned
	skin of any localization	tendency		
2	Dehuliation of damaged skin, single superficial bites or scratches of the trunk, upper and lower extremities (except for the head, face, neck,	A) healthy	healthy	Not assigned
		B) healthy	Got sick, died, disappeared	Start treatment with the appearance of signs of animal disease or disappearance of the animal: 1.0 ml of vaccine on days 0, 3, 7, 14, 30 and 90



	hand, fingers and toes, perineum, genitals), caused by			
		C) with suspected rabies	healthy	Start treatment immediately. 1.0 ml of vaccine for 0, 3, 7, 14, 30 and 90 days. Treatment is discontinued if the animal remains healthy for 10 days of observation.
		D) sick with rabies, ran away, killed		Start treatment immediately. 1.0 ml of vaccine for 0, 3, 7,
	machine animals.	then, the diagnosis is unknown		14, 30 and 90 days.
3	Glaze of the mucous membranes; any salivation of damaged skin, scratches, injuries, bites of the head, face and neck, hand, hands and	A) healthy or with suspected rabies	healthy	Start combination treatment immediately: rabies immunoglobulin (see Notes, item 5) on day 0 + 1.0 ml vaccine on days 0, 3, 7, 14, 30 and 90. Treatment is stopped if the animal remains healthy for 10 days of observation.

	feet. perineum, genitals; multiple bites and extensive damage to any localization; single deep bites and scratches by pets			
		B) healthy or with suspected rabies	Got sick, died, disappeared	Start combination treatment immediately: rabies immunoglobulin (see Notes, item 5) on day 0 + 1.0 ml vaccine on days 0, 3, 7, 14, 30 and 90.
		C) the patient with rabies, escaped, killed, the diagnosis is unknown		Start combination treatment immediately: rabies immunoglobulin (see Notes, item 5) on day 0 + 1.0 ml vaccine on days 0, 3, 7, 14, 30 and 90.

Deputy Minister A. Moskvichev 19.VII.1993

**INSTRUCTIONS \* for the use of rabies immunoglobulin  
from horse blood serum liquid Immunoglobulinum antirabi-  
cum ex sero eqvi fluidum**

Antirabies immunoglobulin from horse blood serum liquid is a protein fraction of the horse's immune blood serum obtained by the rivanol-alcohol method.

The titer of specific antibodies is not less than 150 IU / ml.

The stabilizer is glycol.

The drug is a transparent or slightly opalescent liquid, colorless or slightly yellow in color. Pink staining of the preparation is not allowed.

**IMMUNOLOGICAL PROPERTIES**

Antirabies immunoglobulin has the ability to neutralize the virus both in vitro and in vivo. **PURPOSE**

It is used in combination with rabies vaccine to prevent people from getting sick with severe bites from rabid or suspicious animals.

**METHOD OF APPLICATION AND DOSAGE**

Immediately or as soon as possible after a bite or injury, a local wound treatment is performed. Wounds are washed abundantly with soap and water (detergent) and treated with (40-70) ° alcohol or iodine tincture.

After local treatment of the wound, specific treatment begins immediately. Before injection, check the integrity of the ampoules and the presence of markings on them. The drug is not suitable for use in ampoules with impaired integrity, labeling, as well as when its physical properties (color, transparency, etc.) change, with an expired shelf life, with improper storage.

The opening of the ampoules and the procedure for introducing the drug are carried out in strict observance of the rules of asepsis and antiseptics.

Rabies immunoglobulin is administered at a dose of 40 IU per 1 kg of body weight of an adult or child. Example: body weight of the victim 60 kg; immunoglobulin activity (indicated on the package label). For example, 200 IU in 1 ml.

In order to determine the dose of immunoglobulin required for administration, the weight of the victim (60 kg) must be multiplied by 40

ME and the resulting number should be divided by the activity of the drug (200 ME), that is:

$$60 \times 40 = 2400$$

$$\frac{2400}{200}$$

Before the introduction of antirabies immunoglobulin, to detect sensitivity to a foreign protein, an intradermal test with diluted 1: 100 immunoglobulin (ampoules are marked in red), which is in the box with the drug (ampoules are marked in blue), is mandatory.

The diluted immunoglobulin is injected at a dose of 0.1 intradermally into the flexor surface of the forearm.

The test is considered negative if, after 20 minutes, swelling or redness at the site is less than 1 cm. The test is considered positive if the swelling or redness reaches 1 cm or more.

If the reaction is negative, 0.7 ml of diluted

1: 100 immunoglobulin. In the absence of a reaction, after 30 minutes, the whole dose of immunoglobulin is injected in 3 divided doses with an interval of 10-15 minutes, the entire dose of immunoglobulin heated to (37 ± 0.5) ° C is injected, taking the drug for each portion from previously unopened ampoules.

The calculated dose of immunoglobulin should be injected around and deep within the wound. If the anatomical location of the injury (fingertips, etc.) does not allow the dose to be administered around the wounds, then the remainder of the immunoglobulin is injected intramuscularly into places other than the vaccine (muscles, buttocks, upper thigh, forearm).

The entire dose of rabies immunoglobulin is administered within one hour. The most effective is early administration of the drug, in the first days after injury.

With a positive intradermal test (swelling or redness of 1 cm or more) or in case of an allergic reaction to subcutaneous injection, immunoglobulin is administered with special precautions. First, it is recommended to inject a diluted 1: 100 drug into the subcutaneous tissue of the shoulder in doses of 0.5 ml, 2.0 ml, 5.0 ml with an interval of 15-20 minutes, then 0.1 ml of undiluted immunoglobulin and in 30-60 minutes intramuscularly the entire prescribed dose of the drug, warmed up to (37+0.5) ° C, divided into 3 doses with an interval of 10-15 minutes. Before the

first injection, parenteral administration of drugs (suprastin, diphenhydramine, etc.) is recommended. In order to prevent shock, simultaneously with the introduction of immunoglobulin, subcutaneous administration of 0.1% epinephrine solution or 5% ephedrine solution at an age-specific dosage is recommended.

When administering antirabies immunoglobulin, solutions of epinephrine, ephedrine, diphenhydramine or rastin soup should always be ready.

To prevent complications of an allergic nature after the administration of immunoglobulin, it is necessary to prescribe orally antihistamines (suprastin, diphenhydramine, diprazil, fenkarol, etc.) at an age dosage 2 times a day for 7-10 days.

To the victim who has received tetanus toxoid within the next 24 hours, rabies immunoglobulin is injected without preliminary setting an intradermal test. After the administration of rabies immunoglobulin, the patient must be under medical supervision for at least 1 hour. The vaccination carried out is registered in the established registration forms with an indication of the dose, date, manufacturer of the drug, batch number, reaction to administration.

#### REACTION TO ADMINISTRATION

Injections of rabies immunoglobulin can be accompanied by the development of allergic reactions, including anaphylactic shock and serum sickness.

#### CONTRAINDICATIONS

There are no contraindications. In case of a positive reaction to the administration of anti-rabies immunoglobulin, as well as in the presence of a history of severe allergic reactions to the administration of tetanus toxoid or other preparations of horse serum, the administration of anti-rabies im-

munoglobulin is recommended in a hospital provided with resuscitation means.

#### RELEASE FORM

Antirabic immunoglobulin - 5 or 10 ml in an ampoule, diluted 1: 100 ml in an ampoule.

Produced in a set: 1 ampoule of immunoglobulin and 1 ampoule of immunoglobulin diluted 1: 100.

5 sets - in a cardboard box. The package contains instructions for use and an ampoule knife.

#### SHELF LIFE. STORAGE AND TRANSPORTATION CONDITIONS

Shelf life is 2 years.

Storage - in closed, dry, dark rooms at a temperature ( $5 + 2^{\circ}\text{C}$ ).

Transportation - by all types of covered transport in conditions excluding freezing and heating above  $20^{\circ}\text{C}$ ,

Complaints about the physical and other properties of the drug should be sent to the RGISK im. L.A. Tarasevich (121002, Moscow, Sivtsev Vrazhek, 41, tel. : 541-39-22) and the address of the manufacturer of the drug. Cases of increased reactogenicity or the development of severe complications should be reported by phone or telegraph, followed by the submission of medical documentation to the Russian State University of Emergency Medicine. L.A. Tarasevich.

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