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CURRENT TOPICS

Clinical Features and Management of Human Monkeypox

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Abstract

The COVID-19 pandemic is abating, but the threat of a new epidemic is growing due to the spread of monkeypox in non-endemic regions of the world. In 2022, there were the monkeypox outbreaks throughout Europe, in the Western Hemisphere. With the cessation of the vaccine, due to the global eradication of smallpox, outbreaks of monkeypox have become more common. Currently, there are no exact recommendations for complex treatment and alleviation of the monkeypox symptoms for infected people. Under these conditions, it is especially important to know the pathogenetic mechanisms and epidemiology of the virus for the most effective containment of its spread, especially in view of the negative experience gained in combating the COVID-19 epidemic. The purpose of this study was to summarise the known data on the epidemiology, clinical course and treatment of monkeypox, as well as an attempt to assess the possibility of a new world-spanning pandemic. A targeted search was performed on the keywords "monkeypox", "virology", "Tecovirimat", "Cidofovir", "Brincidofovir" in PubMed, in the period up to July 2022. 661 articles were reviewed, among them as reviews, original research and clinical trials. Preference was given to articles in English that dealt in most detail with cases of monkeypox infection outside the Africa and included comments on the therapy. Seventeen articles were selected and analysed, as well as links within them for additional information on the case. It was revealed that monkeypox is mainly treated with maintenance therapy and the treatment of more complex cases is based on the use of specific antiviral drugs: Tecovirimat, Cidofovir, Brincidofovir. However, there is no widespread therapeutic practice for these drugs. Little is currently known about the monkeypox virus; the transmission of infection, the animal reservoirs, the host range and the prospects for specific treatment are not fully understood. Sharing resources and data with outbreak tracking around the world will greatly facilitate the process of learning about the virus and how to deal with it effectively.

Key words: Monkeypox; Pandemic; *Poxviridae*; Tecovirimat; Cidofovir; Brincidofovir.

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Introduction

In 1958, the smallpox virus was identified for the first time in primates kept as experimental animals in Denmark.[1] The first case of human infection was reported in 1970 in the Democratic Republic of the Congo.[2] Over the past 50 years, sporadic outbreaks have been reported mainly in African countries, they amounted to some thousands. Separate outbreaks of the disease were observed during the importation of animal reservoirs outside the African continent or during the trips to endemic areas and further importation outside them.[3] It has long been feared that zoonotic poxviruses could eventually spread and occupy the ecological niche vacated

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by the killed smallpox.[4] Due to deforestation, population growth and the resulting expansion of living space, due to the encroachment on the habitats of animal reservoirs, as well as increased interstate relations and globalisation, the threat of the monkeypox spread has become much more real over the past 20 years.[5]

It is difficult to predict how the disease will proceed in non-endemic areas, due to the data scarcity on viral kinetics and the duration of the viral shedding. Although the virus has been given the name "monkeypox", primates are not the source of the virus and its true origin is still unknown. There are no approved and licensed treatments for this infection and maintenance care is usually assigned for alleviation of symptoms. The oral drugs Brincidofovir and Tecovirimat have approved themselves for the most severe cases.

The increase in the number of cases during the current outbreak requires updating the knowledge of this infection, in particular about prevention measures, clinical course and epidemiology, in order to prevent large-scale consequences if new outbreaks arise and spread.

The purpose of this study was to summarise the known data on the epidemiology, clinical course and treatment of monkeypox. The research objectives included the droplet spread and non-percutaneous channel of infection, the prospects for the use of specific antiviral drugs and their side effects.

Methods

A targeted search was performed on the keywords, "monkeypox" and "virology", or "Tecovirimat", or "Cidofovir", or "Brincidofovir" in PubMed, in the period up to July 2022. Articles, national recommendations, literature reviews, clinical cases were reviewed. Out of 661 articles, preference was given to reviews and clinical cases written in English, in which the mechanisms of transmission and methods of treatment were most fully disclosed. Eventually, 17 articles were selected and analysed and the accompanying references were checked for additional information on the case.

Results

The *Poxviridae* family is represented by double-stranded DNA viruses that mainly infect animals: mammals, birds, reptiles and even insects. *Poxviridae* is divided into two subfamilies: *Chordopoxvirinae* (18 genera and 52 species) and *Entomopoxvarinae* (4 genera and 30 species). Thus, according to taxonomy, the monkeypox virus belongs to the *Poxviridae* family, the *Chordopoxvirinae* subfamily and the *Ortopoxvirus* genus. Orthopoxviruses are large (140-450 nm) viruses with a genome consisting of approximately 200-500 thousand base pairs.[6] The infectious virus replication cycle can be initiated both by a mature virion and by a cell-free virion that is still enveloped. Glycosaminoglycans, which are located on the cells of all mammals, play the greatest role in binding virions to the cell membrane; however, all receptor sites and their role in interaction with the virus have not been fully characterised (Figure 1).[7]

The monkeypox is endemic in tropical regions of West and Central Africa, especially in the Central African Republic, the Republic of Côte d'Ivoire, Democratic Republic of the Congo, Liberia, Nigeria and Sierra Leone.[4] Cases outside endemic countries are usually associated with international travel or importation of infected animals.[8] It should be noted that there are two strains of monkeypox, the West African, which is less lethal and infectious and the much more dangerous Central African strain.[5]

As a result of the smallpox immunisation program being discontinued 40 years ago, a great part of the population does not have the cross-immunity from monkeypox that was previously provided by the smallpox vaccine.[9] From 1970 to the present, there has been an increase in the incidence in endemic regions, which initiates sporadic outbreaks of the disease in non-endemic countries (Table 1 and 2). Separate outbreaks were even found in Singapore[10] and Israel. Currently, outbreaks have been reported in Italy,[11] Germany,[12] the UK, South America, the Middle East, Canada and the USA.[13]

Due to the large size of viruses such as monkey smallpox, it is more difficult to break through the host's defences, by having to pass through gap junctions. The large size contributes to the early development of the host's immune response and to survive, orthopoxviruses secrete immunomodulatory proteins, which are divided

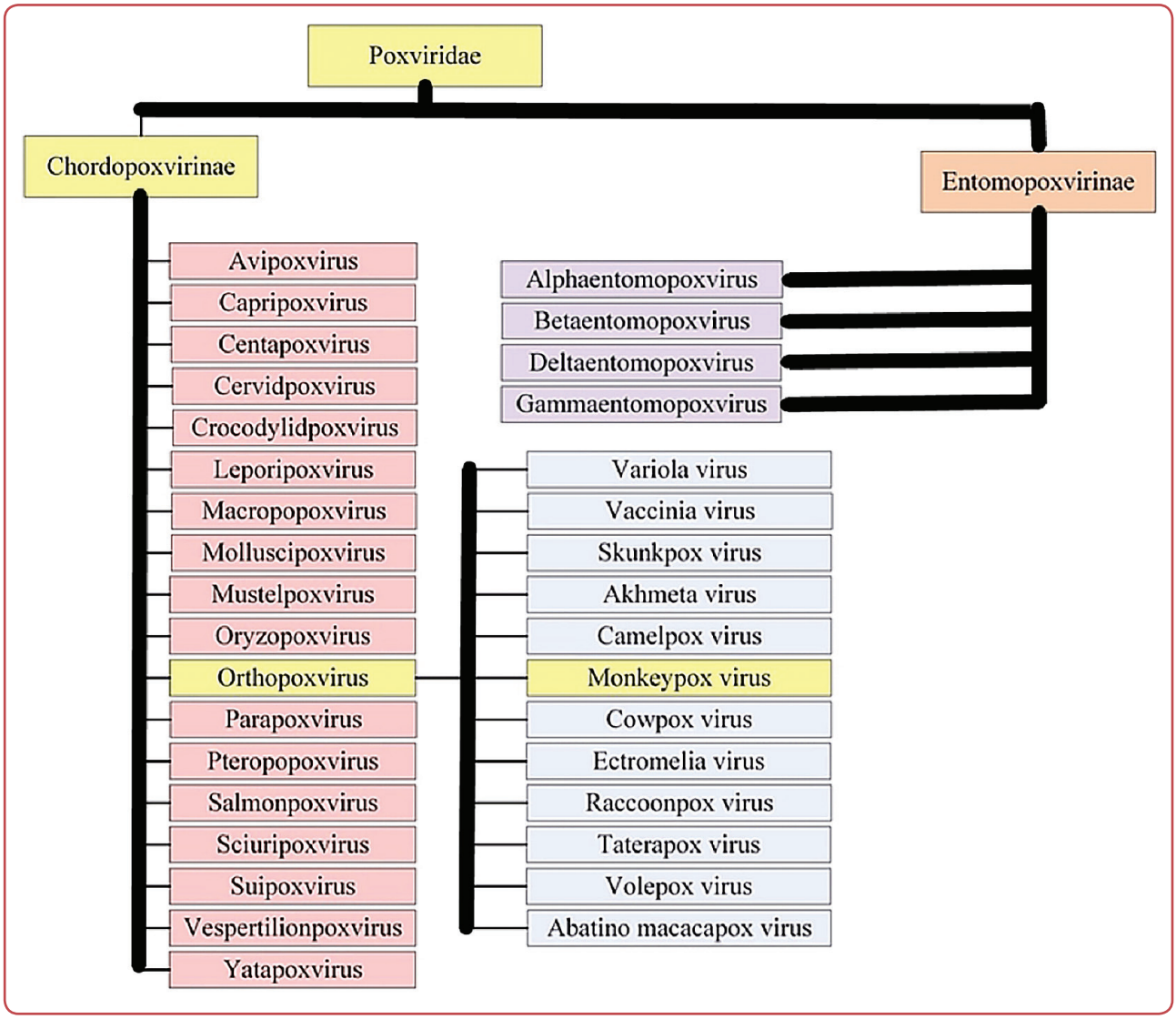

Figure 1: Taxonomy and classification of monkeypox within the family

into two groups - working inside the cell and outside it.[15] The listed proteins, virokines, mimic the activity of cytokines, chemokines and growth factors, thereby allowing the virus to create optimal conditions for the replication and spread of the virus in the body (Figure 2).[15]

The replication cycle of the monkeypox virus is the same as other poxviruses. Both mature and immature virions have an outer membrane that, under the influence of virokines, will bind to glycosaminoglycans or laminin of the host cell. Then, under the influence of additional 12 transmembrane proteins, the viral particle fuses with the affected cell. It is worth noting that mature virions are much more stable than immature ones and mediate animal-to-human transmission, while immature virions are specifically specialised to exit the intact cell and spread within the host.[16]

Table 1: Monkeypox prevalence in endemic countries[14]

Country	Period						Total
	1970-1979	1980-1989	1990-1999	2000-2009	2010-2019	2020-2021	
Central African Republic	-	8	-	-	61	-	69
Democratic Republic of the Congo	38	343	511	10027	18788	7374	37801
Republic of the Congo	-	-	-	73	24	-	97

Table 2: Monkeypox prevalence in non-endemic countries[14]

Country	Period						Total
	1970-1979	1980-1989	1990-1999	2000-2009	2010-2019	2020-2021	
United Kingdom	-	-	-	-	4	-	4
USA	-	-	-	47	-	2	49

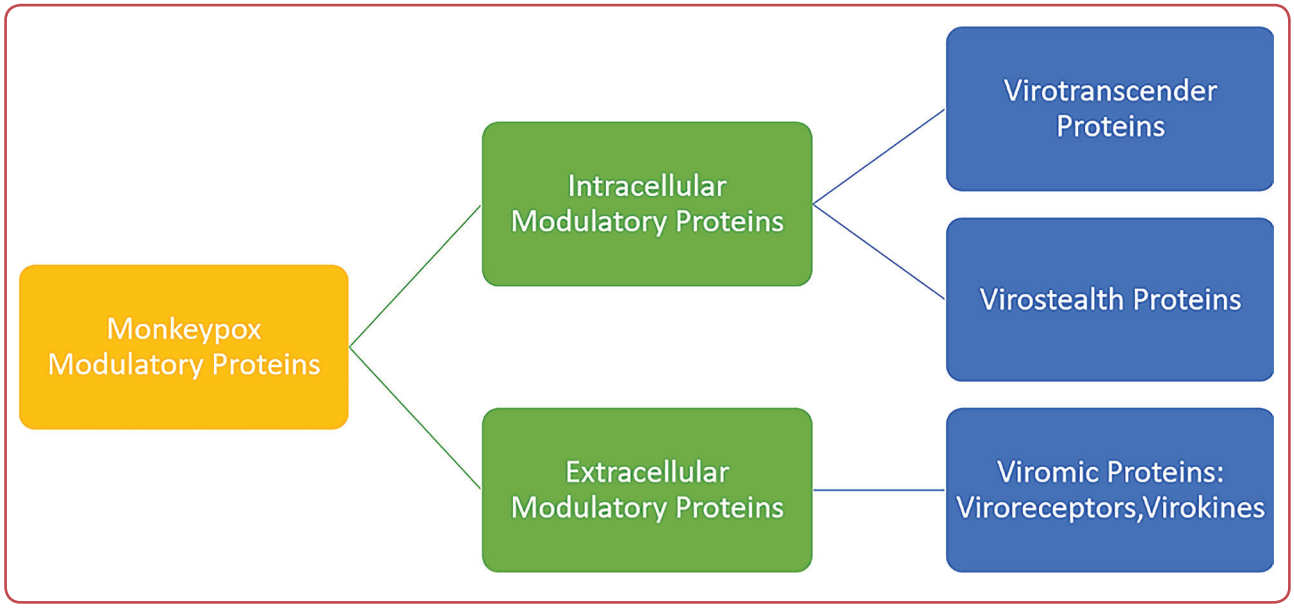

Figure 2: Classification of viral modulatory proteins

Upon entering the cell, the virus forms new structures for replication, known as Guarnieri bodies, commonly called "factories". Each "factory" is a compact DNA structure, surrounded by membranes, which were transformed by the virus from the rough endoplasmic reticulum. As the viral DNA replicates, Guarnieri bodies enlarge, viral mRNAs and host cell translation factors increase in them that promote the rupture of endoplasmic reticulum membranes and the breakthrough of immature virions outside the affected cell (Figure 3).[17]

The monkeypox virus was first identified in Denmark, in a colony of macaques imported for experiments, but animal reservoirs and transmission mechanisms remain unknown. It has been proven that in intermediate hosts the virus can be transmitted from one animal to another and subsequently to humans.[1] It is likely that the reservoir is one or more species of rodents or squirrels found in the forests of Central Africa.[18]

The monkey smallpox virus is thought to have

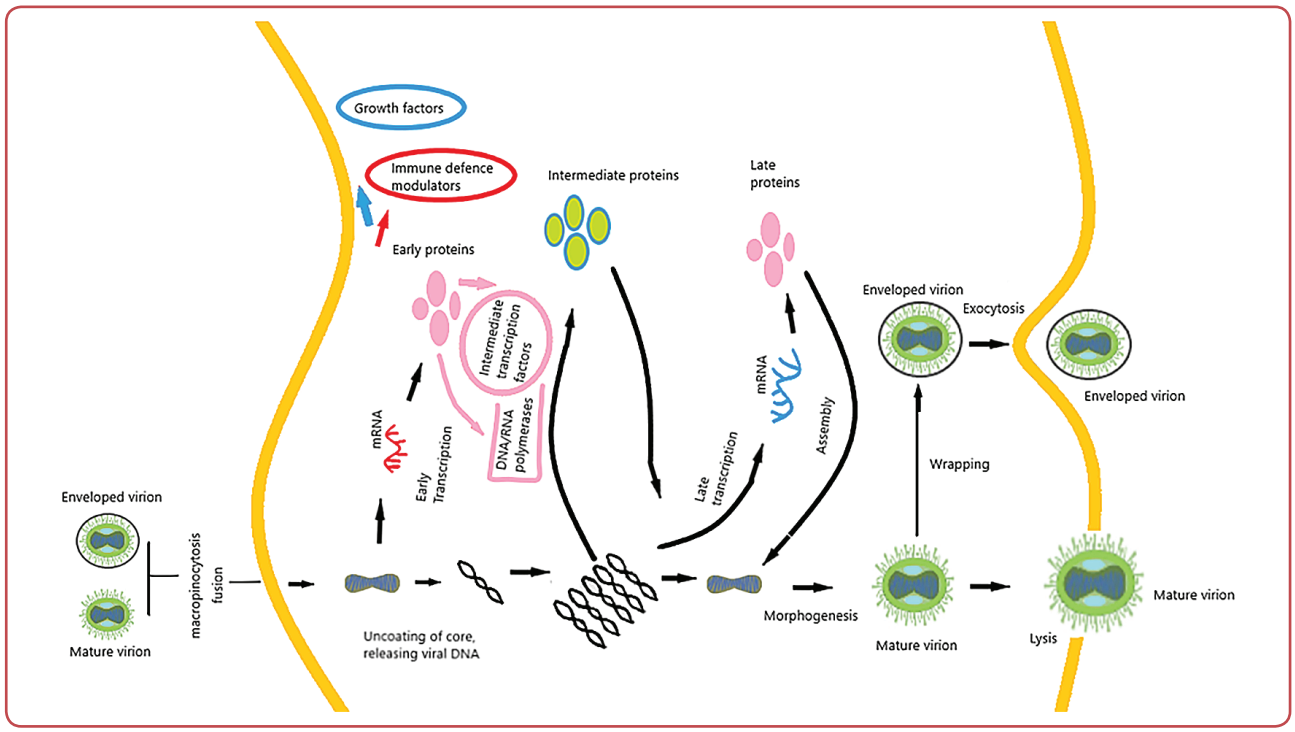

Figure 3: Illustration of the Monkeypox virus life cycle

several transmission mechanisms; in any case, they are associated with direct contact with infected animals or humans. The main monkeypox transmission mechanism is still unknown, but it is assumed that the virus is transmitted with fluids, for example, saliva, by contaminated surfaces and by direct contact, with animal faeces, with sores on the body, mucous membranes (Figure 4).[4]

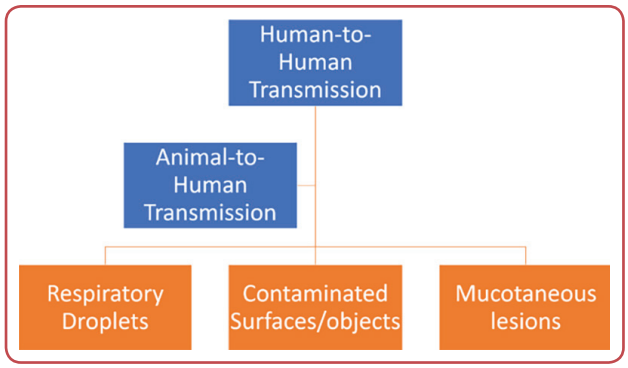

Figure 4: Human-to-human and animal-to-human transmission routes

Although human-to-human transmission is much less common than animal-to-human transmission, it usually occurs by airborne transmission through prolonged contact with an infected person.[19] Amid the current monkeypox epidemic, the disease has been found to be more common in men who have sex with men. According to the World Health Organization, it is not yet known if monkeypox is sexually transmitted or not, but transmission can be attributed to close contact.[15]

Monkeypox virus follows the same transmission as smallpox, beginning with exposure to the mucosa of the oropharynx or respiratory tract of the host. After entry, the virus replicates in the place of invasion and then spreads to the local lymph nodes. With an increase in viral load, the secondary viremia sets in - with the spread of virions to distant lymph nodes and internal organs. The incubation period is usually 7 to 14 days with a maximum of 21 days.[20]

There are no clinical aspects during the incubation period; the infected person is not contagious to others. The symptoms and clinical manifestations of monkeypox occur in the prodromal stage, when the infection spreads from the lymphoid organs to the skin and tertiary organs such as the lungs, eyes, gastrointestinal tract, etc during the course of secondary viremia. It is during the prodromal period that a person is considered most contagious. This is largely due to the occurrence of mucocutaneous lesions and lymphadenopathy, which stand out among other, less specific symptoms.

General, nonspecific symptoms begin to develop one to two weeks after human infection with monkeypox virus.[21] During the prodromal stage, nonspecific symptoms appear: fever, lymphadenopathy, myalgia. Due to its nonspecific nature, an infected person may attribute these symptoms to seasonal flu or the common cold. A signature of the disease during this period, which may alert the patient, is the synchronous enlargement of the maxillary, cervical and inguinal lymph nodes.[15] In some patients, these symptoms may be mild or not present at all.[20] In typical cases, the fever often subsides the next day or within three days of the breaking-out. The rash first appears on the face and quickly spreads throughout the body from the centre to the periphery.[22] The rash usually has a well-defined shape. By nature, it is a disseminated blistering-pustular rash.[23] The rash itself goes through several stages: the stage of enanthem, macule, papule, then vesicle and pustule, after which they flake and scab over. Once the crusted lesions slide off, the human is no longer considered contagious.[24]

A certain discomfort to the patient is caused by gastrointestinal symptoms that occur by the second week of the disease. These are vomiting and diarrhoea, they contribute to significant dehydration in the infected person. The most serious complication of monkeypox is infection of the cornea. The development of concomitant eye infections can lead to the formation of scars on the cornea and irreversible loss of vision. The tendency to more severe course, with the development of more complications, is noted in patients who are not vaccinated against smallpox (74 %); vaccinated patients are significantly less likely to get complications (39.5 %).[22] After the elimination of smallpox, vaccination of the population was not carried out. Thanks to cross-immunity, people who were vaccinated against smallpox before the 1970s are much less likely to get complications from monkeypox infection. Separately, it is worth considering the phenomena of sepsis and septic shock, which are associated with an excessive immune response.[15] However, monkeypox is a self-limited viral disease and very rarely causes lifelong complications.

Although bronchopneumonia is a complication of monkeypox infection, it occurs more frequently in persons co-infected with influenza virus.[15]

It has been shown that lung disease in non-human primates in the range of infectious doses leads to the development of focal lung tissue necrosis, diffuse lung consolidation and peracute bronchopneumonia.[23]

The clinical treatment of monkeypox is based on maintenance therapy, which includes maintaining fluid balance, haemodynamic support, respiratory support, treatment of associated skin and mucosal infections, usage of lubricants and topical antibiotics to prevent eye damage.[23, 25] There are currently no specific drugs approved for the treatment of monkeypox. However, a number of antiviral drugs have shown their effectiveness. Such drugs are Cidofovir, Tecovirimat, Brincidofovir.[26]

Table 3: Methods of laboratory diagnostics

Method	Point of application
Culture-based	Possibility of obtaining a pure culture of the virus for final verification. Orthopoxviruses form characteristic bodies on chorioallantoic membranes.
Electron microscopy	In the negative, a clear image of Paschen's corpuscles is obtained. The method is used to identify viral particles in samples.
Immunohistochemistry	Used to identify antigens in samples. Used as an exclusion method when identifying other suspicious agents.
Real time PCR	The method detects viral DNA and can identify active infections using material taken from the patient.
Test for IgM	Used to assess recent exposure to orthopox-virus and in suspected patients previously vaccinated against smallpox.
Test for IgG	Used to assess the duration of exposure to orthopoxvirus, including vaccination.
Tetracore Orthopox Bio-Threat Alert	Test for the detection of antigens to orthopox-virus. Can quickly identify an active case using patient material taken on sight, does not require specific skills.

For the monkeypox virus detection (Table 3), it is necessary to combine laboratory diagnostic methods,takeintoaccountclinicalsymptomatology and epidemiological anamnesis and the patient's vaccination history. Samples for detection of the virus can be blood, urine, swab from the upper air passages, scrapings with discharge from papules. Traditional diagnostic methods, such as culture-based, immunohistochemistry, microscopic examination, require appropriate qualifications and can only be carried out using specialised equipment in a modern laboratory.[27] For retro-spective study analysis, it is recommended to use immunotechnique and serological diagnostic methods based on the detection of antibodies to orthopoxviruses, since they have cross-reactivity. These methods should be actively applied in endemic areas and areas where there have been outbreaks of monkeypox. At the same time, it should be noted that the presence of acute phase immunoglobulins - IgM to orthopoxvirus virions and not IgG indicating a long-term infection, is revealed in the samples. The presence of the latter in the probe is nonspecific because it may indicate lifetime exposure of the virus, or vaccination.[28] The real-time polymerase chain reaction (PCR) method, which has the highest sensitivity, seems to be the most optimal for early diagnosis at the moment. However, this method can also be used in the presence of a highly technologically equipped laboratory. In conditions of limited resources, the method is not applicable.[29] Unfortunately, the main burden on the use of resources is the arrangement of conditions for the collection and storage of samples, so there was a need for tests for detection in the field with minimal training. In this regard, a test (*Tetracore Orthopox BioThreat Alert*®) was developed in 2003.[30]

Cidofovir was approved by the Food and Drug Administration (FDA) in 1996 for the treatment of patients with retinitis caused by Cytomegalovirus (CMV), patients with acquired immunodeficiency syndrome. Cidofovir has broad antiviral activity against viruses from different families, including herpes viruses, adenoviruses and poxviruses. This drug was used as part of a treatment regimen for a 28-month-old boy with refractory atopic dermatitis who got severe eczema *vaccinatum* after contact with a smallpox-vaccinated father.[31] The child survived and there were no long-term after-effectiveness.

Tecovirimat is the first antiviral drug indicated for the treatment of smallpox in adults and children weighing at least 3 kg. It was approved by the FDA in 2018 and in January 2022, it was recognised as effective by the European Medicines Agency. It has been used in several case reports to treat disseminated and ocular cowpox[32, 33] and cowpox infections as part of a multidrug regimen.[34] Tecovirimat was used to treat a patient with imported monkeypox in the United States in 2021.[8] In a recent case series, 1 out of 7 patients received Tecovirimat for 2 weeks. No side effects were noted, but a shorter duration of viremia was achieved.[35] In a report of the first 17 patients with confirmed monkeypox in the US during the ongoing 2022 outbreak, 1 patient took Tecovirimat.[36]

Table 4: Comparative characteristics of antiviral drugs used against monkeypox

Name	Routes of administration	Mode of action	Side effects	Safety precautions	Contraindications
Tecovirimat	Orally, intravenously. Single dose. Adults: 600 mg. Children weighing 13 kg to less than 25 kg: 200 mg. Children weighing 25 kg to less than 40 kg: 400 mg. Children weighing 40 kg or more: 600 mg. Taken 2 times a day for 14 days.	Inhibitor of the orthopoxvirus VP37 envelope wrapping protein	Headache, nausea, abdominal pain, vomiting. Infusion site reactions may occur with the intravenous form	Dose adjustment of Tecovirimat is not necessary while treating patients with a kidney or liver disease when taken orally. When administered intravenously, it should not be given to patients with severe renal insufficiency.	No
Brincidofovir	Adults weighing 48 kg or more – 200 mg once a week for 2 doses. Adults and children weighing 10 kg to less than 48 kg – 4 mg per kg of body weight once a week for 2 doses. Children weighing less than 10 kg – 6 mg per kg of body weight once a week for 2 doses.	Phosphorylated to the active metabolite, Cidofovir diphosphate, which selectively inhibits viral DNA synthesis mediated by orthopoxvirus DNA polymerase	Diarrhoea, nausea, vomiting and abdominal pain	Not recommended for pregnant and lactating women (before treatment, a pregnancy test should be performed in women of childbearing age). May cause an increase in the activity of transaminases and bilirubin in serum.	No
Cidofovir	5 mg/kg once weekly for 2 consecutive weeks, then 5 mg/kg intravenously once every two weeks	It undergoes cellular phosphorylation, then selectively inhibits viral DNA synthesis mediated by orthopoxvirus DNA polymerase.	Decreased serum bicarbonate, proteinuria, neutropenia, infection, ocular hypotony, iritis, uveitis, nephrotoxicity, fever	Dose adjustment required depending on renal function	Must not be initiated in patients with serum creatinine > 1.5 mg / dL, calculated creatinine clearance (Clcr) ≤ 55 mL / minute, or urine protein concentration ≥ 100 mg / dL; with allergic reactions

Brincidofovir has been approved for the treatment of smallpox in the US since June 2021.[37] Brincidofovir, when administered orally, performs better than intravenous Cidofovir, as it has less nephrotoxicity. The drug has approved itself for patients with adenovirus,[38] CMV infection[39] and poxvirus infections. Brincidofovir was used in combination therapy in a patient with acute myeloid leukaemia and developed smallpox due to a recent vaccine after induction chemotherapy. In addition to other drugs, the patient took 6 doses of Brincidofovir.[34] The drug has also been used in a 17-year-old patient who got a fatal cowpox infection after a kidney transplant.[40] In May 2022, the clinical management of 7 monkeypox patients in the UK was described. In this case series, 3 patients received Brincidofovir. However, due to an increase in hepatic enzymes (a side effect of the drug), treatment had to be discontinued.[35]

The FDA approved immunoglobulin against cowpox in 2005 for the treatment of complications of cowpox vaccination.[41] This intravenous drug has appeared relatively recently. Its predecessor was intended for intramuscular administration and therefore had less effectiveness.[42] An FDA-approved intravenous form of immunoglobulin has been used in several reports, such as in a patient with inflammatory bowel disease and developed infection after exposure to a recombinant antirabic vaccine based on the vaccinia virus. Immunoglobulin has also been used to treat two patients with developed symptoms of cowpox after contact with a man who had had the virus transmitted sexually from a recently vaccinated sexual partner.[43]

Discussion

The neglect of monkeypox in humans is mostly benign and moderate, with a tendency for the virus to self-limit. The introduction of antiviral therapy into the treatment course should be considered in cases of especially severe disease, eye-lesion, oral or perineum lesions, in patients

with a risk of the disease becoming severe (ie, immunocompromised persons, children under the age of 8, pregnant and breastfeeding women, patients with atopic dermatitis or other active skin conditions).[24]

Currently, there is the greatest clinical experience with Tecovirimat, therefore it is preferred. Ideally, the treatment of monkeypox should be carried out in the context of clinical trials, this is necessary to obtain long-term evidence that could provide information about the prospects for such treatment and the opportunity of adjusting it in process based on the evidence base. Therefore, clinicians are encouraged to coordinate management programs and approaches with infectious disease experts and public health authorities.
The mode of virus transmission, its tendency to self-limit, suggests that contact tracing is crucial in the fight against the monkeypox spread. For identification of the circle of contacts and potentially infected persons, it is necessary to question the patient in detail. Emphasis should be made on the nature of contacts: their duration, degree of closeness (whether it was face-to-face conversation or direct (including sexual), physical contact or contact with contaminated surfaces (bedding, shared objects). It must not be forgotten the possibility of animal-to-human transmission: if the patient had contact with a pet, the pet should be isolated for 21 days.

In order to prevent the infection spread in a medical facility, everyone who had contact with the patient (staff, hospital roommates, visitors) should be identified. If someone has been in contact with a person with monkeypox, attention should be paid to the presence of symptoms such as fever, rigor, rash and lymphadenopathy occurring within 21 days of the last contact. The asymptomatic course of the incubation and prodromal period has been repeatedly reported, therefore, everyone who has been in contact with the patient should be considered potentially infected.[19]

On 14 May 2022, 2 cases of monkeypox infection were reported in the UK in one family; patients have never been in endemic areas. Thousands of cases have been reported in many countries in Europe, South America, the Middle East, Canada and the United States. The virus mainly affected men between the ages of 25 and 35, mostly among those who self-identify as homosexual or bisexual.[13] It is not completely known whether the virus is transmitted sexually in a traditional sense, or whether close contact with an infected person plays a big role, although small amounts of the virus have been isolated from the semen of patients in Italy[11] and Germany.[12]

The ongoing global outbreak of monkeypox is one of the largest in history. The transmission chains are occurring in many non-endemic countries. This fact indicates that the virus transmission, due to the length of the incubation period, remained unnoticed for a long time. This contributed to the creation of significant clusters of infected people, who, even in the prodromal period, due to the nonspecificity of symptoms, did not arouse suspicion among clinicians. This situation allows us to draw a parallel with the barely abated COVID-19 pandemic, also a zoonotic virus that spread in a similar way. It seems unlikely that the monkeypox virus could cause a global epidemic on the scale of the COVID-19 pandemic. However, the severity of the looming threat should not be underestimated. A long incubation period, the scarcity of the arsenal of drugs for adequate and timely treatment, blind spots in the understanding of the virus transmission mechanisms in the population make the threat real.

Studying the trends and characteristics of the current outbreak will be key to identifying the tools needed to contain it. Implementing screening in healthcare facilities and maintaining a high level of suspicion will help identify new cases and determine the extent of the outbreak. Early isolation of suspected and confirmed cases of infected persons, as well as close monitoring and vaccination of their relatives and high-risk healthcare workers as needed, will help break the chains of the virus transmission. Monkeypox has a wide host range, which gives it the potential to enter new ecological niches and if the current outbreak drags on, there are significant concerns about the emergence of new endemic areas outside of Africa.

Conclusion

Thus, little is currently known about the nature of the monkeypox virus. The exact transmission mechanism, reservoir animal, host

range and specific treatment prospects have many blind spots. Hope is that in time it will be possible to shed light on them.

The current outbreak of monkeypox is the largest seen in recent decades. It is important to prevent the emergence of a new pandemic, so it is needed to act quickly and decisively. Lessons should be learned from recent epidemics and available resources and information should be shared as early as possible. Monkeypox is becoming a global public health problem. The time has come to approach this problem globally and eradicate the infection not only in rich countries, but also in endemic regions. Only in this way can we protect ourselves and future generations from this dangerous disease.

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Conflict of interest

None.

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