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Coxsackie Virus and its Effect on Human Health: A review

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Abstract

In low- and middle-income countries, coxsackievirus infections constitute a serious public health concern, especially for young children and newborns. Many human ailments, such as hand, foot, and mouth disease, as well as diseases of the heart, lungs, and muscles, are brought on by these infections, which are common around the world. Coxsackie virus infections typically cause mild flu-like symptoms and resolve on their own. However, in certain situations, they might progress to more serious diseases. According to previous studies, around 50% of affected children do not exhibit any symptoms. Others experience a sudden high temperature, muscle aches, and headache; some also experience nausea, stomach pain, or sore throats. Coxsackievirus infections have a brief incubation period, lasting one to five days. A youngster with a Coxsackievirus infection may only feel hot and have no other symptoms. Most children's fevers endure around three days and then disappear.

In this review, we will provide a brief virus from its initial discovery to the laboratory techniques used to diagnose it, in addition to reviewing the epidemiological data, which offer detailed information on the diversity and distribution of the many Coxsackievirus types. We will also highlight the most important disease it causes, which is hand, foot, and mouth disease.

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1. Introduction

Coxsackieviruses (CVs) are members of the Enterovirus genus, which in turn belongs to the Picornaviridae family. Dr Gilbert Daldorf (a scientist at the New York State Department of Health) isolated the virus in 1948-1949, and it was called after the place where it was discovered, Coxsackie, which lies south of Albany in New York [1-3]. Enteroviruses (EV) are the most important and prevalent human infections. They affect people of all ages, but they are more common in children [4].

The Internal Committee on Virus Taxonomy classifies the EV genus into 15 species (12 EV species (EV-A to EV-L) and 3 Rhinovirus species) [5]. Four (A–D) of the 12 EV species are known to infect humans; they include (poliovirus, CV (CVA and CVB), echovirus, and EVs serotypes [6]. CVs are non-enveloped, positive-sense, tiny (~30 nm) viruses with linear single-stranded RNA. Their genome is contained in icosahedral symmetric naked capsids as shown in Figure 1 [7,8]. Coxsackievirus is classified into two groups: A and B. Both groups of viruses are primarily spread through the fecal-oral pathway and respiratory droplets and cause symptoms of upper respiratory tract infection, fever, and rash. Infection with the CV is widespread and more prevalent in higher latitude regions. The most vulnerable are immunocompromised people and newborns [4,53].

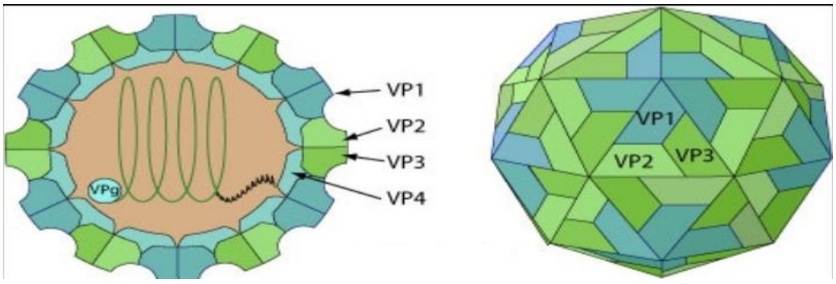

Figure 1. Coxsackie Virus Genetic and Physical Structure [4].

2. Taxonomy

Coxsackieviruses were classified into 29 species until 1999 when two of them were eliminated, and the other ones combined to form other species [9].

Realm: ***Riboviria***
Kingdom: ***Orthornavirae***
Phylum: ***Pisuviricota***
Class: ***Pisoniviricetes***
Order: ***Picornaviruses***
Family: ***Picornaviridae***
Genus: ***Enterovirus***
Species: ***9+*9+-Coxsackievirus***

3. Picornaviridae, Coxsackievirus Family

The fundamentals of virology have been significantly aided by picornaviruses. Coxsackievirus and poliovirus (PV) were among the "ultra-filterable infectious agents" that sparked the field of animal virology [10]. Even with all the knowledge that has been gained, picornaviruses still pose a barrier to our understanding. Picornaviruses pose public health issues and fundamental questions that remain unanswered, suggesting that we are still far from a definitive understanding [11-13]. A vast family of animal viruses known as Picornaviridae can cause both mild and deadly illnesses as well as infections that are clinically silent. The current classification comprises around 30 genera and 75 species, including the human picornavirus genus Enterovirus and other human picornaviruses from the genera Cardiovirus, Cosavirus, Parechovirus, Kubovirus, and Salivirus. Picornaviruses employ their ~7–9 kb positive-sense single-stranded RNA genomes as mRNA for the production of viral proteins and each viral protein's polyprotein precursor is encoded by a single ORF found in its RNA. Notably, the genome's 5′ ends are covalently linked to the viral protein genome (VPg), which is the initiator used in viral RNA synthesis [10,14].

4. Transmission

The Coxsackie virus spreads through human contact and respiratory droplets, which are fluids from coughing and sneezing, and taint the surface. Coxsackie virus can infect people of any age, even though it mostly impacts youngsters younger than 10 and those with compromised immune systems [15]. The primary modes of CV transmission [16]:-

1. When an infected individual coughs or sneezes into the mouth, nose, or eyes, it can spread directly to those areas.
2. Fecal-oral: the virus that an uninfected person's feces carry into their mouth.
3. Via interaction with the surface
4. Through the surface airborne, occurs when a person who is not sick inhales respiratory droplets from a sick person.

5. Pathogenicity

There are two types of Coxsackie viruses: Group A and Group B. Coxsackie viruses are linked to infections of the skin and mucous membranes, acute hemorrhagic conjunctivitis, and hand, foot, and mouth disease (HFMD). Accordingly, Group B is in charge of infections that affect the heart, pleura, pancreas, and liver, causing myocarditis, pericarditis, hepatitis, and pleurodynia [4,52]. By continuously infecting and inflaming pancreatic β-cells, CVBs, and echoviruses are also linked as environmental factors in the etiology of type 1 diabetes [2]. The primary means of transmission for CV infections include respiratory droplets, fomites, and the fecal-oral pathway. Next, the viruses multiply in the lymphoid tissue (tonsils, Peyer's

patches of the intestinal mucosa), small intestine, and oropharynx mucosa. The virus can be detected in feces for up to eight weeks after the first infection and in the respiratory system for up to three weeks [17].

6. Signs and Symptoms

Many diseases can result from the Coxsackie A virus, but symptoms of the flu and fever, skin rashes, and mouth sores are the most typical signs and symptoms of infection. Three to six days after exposure, infected individuals may exhibit a low-grade fever, sore throat, and overall discomfort. There could be painful oral sores behind the mouth called herpangina. Usually starting 24 hours after the flu-like symptoms start, these sores can blister and make eating or drinking more uncomfortable. There may be a flat, red rash on the skin that is frequently followed by blisters filled with fluid and scabbing. The rash typically appears on the palms of the hands, the bottoms of the feet, and other parts of the body. It can last for up to 10 days [18]. Extremely severe symptoms might result in seizures and convulsions from a high fever, or dehydration from the inability to swallow food or fluids without pain, necessitating hospitalization for some people. Dry skin, inadvertent weight loss, decreased urine production, or colored urine are indicators of dehydration, and if these occur, you should see a doctor for treatment. Other serious repercussions include inflammatory brain conditions that require medical attention, such as viral meningitis or encephalitis [19]. If the infected person is immunocompromised or if the symptoms do not get better in Ten days, expert medical attention may need to be provided [16,20,21].

7. Hand, Foot and Mouth Disease

Coxsackievirus is the most common cause of this viral illness, which is generally benign but highly contagious—particularly among young children. Its hallmark symptoms include mouth sores and a rash on the hands and feet. Currently, no specific treatment exists. Preventive measures, such as avoiding close contact with infected individuals and practicing frequent hand washing, can significantly reduce the risk of infection [22]. The incubation period—typically lasting three to six days—is the interval between initial exposure and the onset of symptoms (Figure 2). Early signs often include fever, sore throat, reduced appetite, and general malaise. One to two days after the fever starts, painful sores may appear in the mouth or throat, followed by a rash affecting the hands, feet, and sometimes the buttocks [28]. Transmission primarily occurs through oral ingestion of the virus. Close contact with an infected individual may spread the illness via respiratory droplets from coughing or sneezing, as well as through saliva, blister fluid, stool, and nasal or throat secretions. Because toddlers frequently place their hands in their mouths and undergo frequent diaper changes and toilet training, the infection is especially common in daycare settings. While the illness is most contagious during the first week, the virus can remain in the body for weeks after symptoms have resolved, meaning the individual may still transmit it. Notably, adults can carry and spread the virus without exhibiting any noticeable symptoms. In the United States and other temperate regions, outbreaks are more common during summer and fall, whereas in tropical climates, they can occur throughout the year [24]. Although there is no cure, symptoms generally resolve within seven to ten days [29].

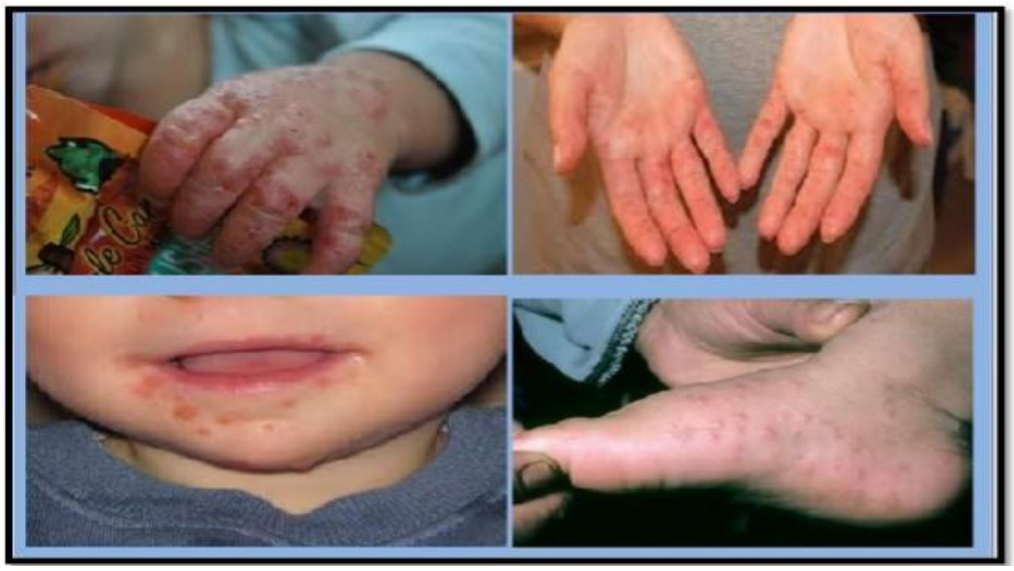

Figure 2. Signs and symptoms of HFMD. The figure shows the clinical and biological signs of CV infection [4].

8. Epidemiology

Researchers in the US town of Coxsackie injected fecal samples from two suspected instances of polio into nursing mice in 1948; the mice's skeletal muscles developed lesions, and the first Coxsackie virus was discovered [4]. HFMD outbreaks in 1991 in Sydney, Australia [30], 1994 in England and Wales [31], 2002–2003 in Taiwan [12], 2002, 2005, and 2007 in Singapore [32], 2005 in Vietnam [33], and 2009 in Odisha, India [34] were caused by CA16 infection. In mainland China, CA16 was the most common pathogen responsible for HFMD in Guangzhou in 2009 [35] and Beijing in 2007 [36].

The most common enterovirus type found was CVB5, which was followed by E30 and E6. E6 in 2015, CVB5 in 2017, and CVB5 and E30 in 2019 epidemics, all three types displayed epidemic trends. Meningitis outbreaks have occurred in different parts of the world linked to E30 and E6 and have been regularly documented. Likewise, there have been prior reports of CVB5 meningitis outbreaks [37]. However, a recent assessment found that CVB5 is only linked to a small percentage of enterovirus-induced neurological diseases worldwide [38]. Children frequently contract HFMD, an infectious disease brought on by EVs of the Picornaviridae family [39]. In India, the first outbreak of HFMD was reported in 2004 [40]. After three years, Kolkata and the neighboring territories of the eastern state of West Bengal experienced their first large-scale outbreak in 2007 [41].

Based on clinical descriptions, other small-scale epidemics have since been reported from various locations [42]. CA16 and EV71 are the primary causal pathogens among the several serotypes linked to HFMD, particularly in severe and fatal cases [43]. CA6, on the other hand, has seldom ever received clinical attention because the infections it causes are usually mild or asymptomatic. However, the circulation of CA6 has increased since the 2008 CA6-associated HFMD outbreak in Finland, and it has been linked to multiple HFMD outbreaks in Asia, Europe, and the USA [22]. According to [23], EV71, CA16, and CA6 are the main causal agents of HFMD, which affects over a million children in China each year. The disease is spread by contact with an infected individual, respiratory droplets released into the air after coughing or sneezing, saliva, blister fluid, respiratory secretions or throat discharge, and person-to-person contact. HFMD is particularly common in children who attend daycare centers because of frequent diaper changes, toilet training, and the frequent putting of hands in their mouths by young children. The first week of HFMD is when the child is most contagious, however, weeks after the symptoms have gone away, the virus may still be present in their body.

According to this, a youngster can still transmit the virus. Certain individuals, particularly adults, might spread the virus without exhibiting any illness-related symptoms. In temperate regions like the United States, outbreaks of the disease are more frequent in the summer and fall, while in tropical regions, epidemics happen all year round [24]. Since EV-A71 and CV-A16 have been identified as the primary causes of HFMD in Japan from 2012 to 2018, it is significant that an increase in cases has been observed every three years, which has been linked to a three-year cycle component of EV-A71 [25]. Nevertheless, a more thorough examination of the etiologic agent distribution also indicates that CV-A16 instances fluctuate over time. Additionally, EV-A71 was the primary cause of Japan's epidemic outbreaks in 2000 and 2003 [26], whereas outbreaks in India and Japan were attributed to CV-A16 [27]. The EV genome has undergone multiple mutations during this time, leading to a variety of genotypes and the alterations that follow. Differences in antigenicity between strains and the potential for recombination among EV types are examples of phenotypic diversity that indicate the creation of new kinds is continuous [25].

9. Diagnosis

Due to the high predictive power of acute fever and rash association in regions where the disease is endemic, CV infections are usually diagnosed clinically [4]. Similar to other EVs, early and timely identification of CVs and genetic characterization are essential components of surveillance plans, particularly for individuals exhibiting severe clinical manifestations. Furthermore, a quick laboratory identification of a CV infection may reduce the need for antibiotics, decrease the period of hospitalization, avoid unnecessary and costly tests, and lessen the likelihood of sequelae. It is crucial to emphasize that depending on the clinical presentation, other clinical specimens may be needed for diagnosis, including stool, nasopharyngeal, cerebrospinal fluid, conjunctival, and oropharyngeal swabs, biopsies, urine, blood, or vesicle fluid [44,45].

9.1 Virus isolation

Historically, cell cultures have been the basis for the isolation and characterization of EVs due to the ability of most of their strains to grow rapidly in these cell cultures. L20B, HEp-2, and RD are among the best cell cultures used for this purpose, especially for the isolation of poliovirus [46]. The cytopathic effects that appear in tissue cultures (shrinkage, visible rounding, refraction, nuclear pyknosis, cell lysis) are evidence of the growth of viruses in these cultures [47].

Virus isolation helps in characterizing the virus, detecting EV co-infection, confirming new EV variants, and evaluating the effectiveness of antiviral agents [45,48]. However, this method of diagnosis has disadvantages, including that it is time-consuming, expensive, requires sufficient expertise, and all CVAs, except for CVA9 and CVA16, do not grow well in cultures. In addition, some EV strains fail to grow in these cell cultures (Schmidt *et al*.,1975; Modlin, 2010).

9.2 Viral antigen detection tests

Rapid POCT chromatography and immunofluorescence testing are two commercially available tests. These assays are rarely used in routine practice because their main drawback is their incapacity to sort EVs [46].

9.3 Serological diagnosis

The PCR and virus isolation techniques for Coxsackievirus isolation require expensive equipment and materials, as well as trained workers with adequate experience, unlike ELISA, which is an easy and inexpensive method for testing large numbers of samples in a short time and is suited for routine work (Mao *et al*., 2014). Numerous commercial ELISA tests are available on the market; some identify the antigen itself, while others identify antibodies to the virus in acute and convalescent serum [47].

9.4 Molecular diagnosis

These assays rely on the identification of viral RNA, and all types of EVs in clinical samples can be diagnosed using reverse transcriptase PCR, which primarily targets the highly conserved 5′ non-coding region [48].

RNA amplification's sensitivity, Like that of all techniques of PCR, varies greatly and is contingent upon the type of sample used. Before DNA extraction, the sample must be handled carefully, particularly fecal samples because they contain inhibitory compounds. Specificity, sensitivity, and quick turnaround time are advantages of PCR-based techniques for the diagnosis and detection of all organisms, including EVs, but recombination at the primer binding sites that some types of these viruses undergo may lead to failure of detection [44,48,49].

Lastly, a crucial part of the diagnosis and monitoring of EV infections is the typing of viruses by sequencing for the VP1 gene utilizing the traditional Sanger technique and, more recently, technologies for next-generation sequencing of the entire genome [45,48].

10. Prevention:-

No vaccine can minimize the likelihood of infection and transmission [50]. To limit the transmission and spread of the virus, non-pharmacological prophylactic measures must be taken. The most effective and best means of prevention include washing hands, avoiding touching mucous membranes, avoiding close contact with infected persons, in addition to sanitizing commonly handled tools and surfaces [16].

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The authors declare that there is no conflict of interest

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The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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فيروس كوكساكي وتأثيره على صحة الإنسان: مقالة

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المستخلص:

تُشكل الأصابة بفيروس كوكساكي في الدول منخفضة ومتوسطة الدخل مصدر قلق خطير على الصحة العامة، وخاصةً للأطفال الصغار وحديثي الولادة. تُسبب هذه العدوى الشائعة حول العالم العديد من الأمراض البشرية، مثل امراض اليد والقدم والفم، بالإضافة إلى أمراض القلب والرئتين والعضلات. عادةً ما تُسبب عدوى فيروس كوكساكي أعراضًا خفيفة تُشبه أعراض الإنفلونزا والتي تزول من تلقاء نفسها. ومع ذلك، قد تتطور في بعض الحالات إلى أمراض أكثر خطورة. ووفقًا للدراسات، لا تظهر أي أعراض على حوالي 50% من الأطفال المصابين. ويُعاني آخرون من ارتفاع مفاجئ في درجة الحرارة، وآلام في العضلات، وصداع؛ كما يُعاني بعضهم من الغثيان، وآلام في المعدة، أو التهاب في الحلق. و تتميز عدوى فيروس كوكساكي بفترة حضانة قصيرة، تتراوح من يوم إلى خمسة أيام. وقد يشعر الطفل المصاب بعدوى هذا الفيروس بالحرارة فقط دون أي أعراض أخرى. تستمر حمى معظم الأطفال لثلاثة أيام تقريبًا ثم تختفي.

في هذه المقالة، سنقدم لمحة موجزة عن كل ما يتعلق بهذا الفيروس، بدءًا من اكتشافه الأولي وحتى التقنيات المخبرية المستخدمة لتشخيصه، بالإضافة إلى مراجعة البيانات الوبائية التي تقدم معلومات مفصلة عن تنوع وانتشار أنواع عديدة لفيروس كوكساكي. كما سنسلط الضوء على أهم الأمراض التي يسببها، وهو مرض اليد والقدم والفم.