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The Crux

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CONTENTS

Editorial

Monkeypox is an infectious viral disease that can occur in humans and some other animals. Symptoms include fever, swollen lymph nodes, and a rash that forms blisters and then crusts over. The time from exposure to onset of symptoms ranges from 5 to 21 days. The duration of symptoms is typically 2 to 4 weeks. There may be mild symptoms, but to what extent it may occur without any symptoms is not known. The classic presentation of fever and muscle pains, followed by swollen glands, with lesions all at the same stage, has not been found to be common to all outbreaks. Cases may be severe, especially in children, pregnant women or people with suppressed immune systems.

The disease is caused by monkeypox virus, a zoonotic virus in the genus *Orthopoxvirus*. The variola virus, the causative agent of smallpox, was also in this genus. Of the two types in humans, the West African type causes a less severe disease than the Central African (Congo Basin) type. It may spread from handling bushmeat, animal bites or scratches, body fluids, contaminated objects, or other close contact with an infected person. Spread can occur by small droplets and possibly the airborne route. People can spread the virus from the onset of symptoms until all the lesions have scabbed and fallen off; with some evidence of spread for more than a week after lesions have crusted. The virus is believed to normally spread among certain rodents in Africa. Diagnosis can be confirmed by testing a lesion for the virus's DNA. The disease can appear similar to chickenpox. The **"DISEASE DIAGNOSIS"** segment outines MONKEYPOX for you.

CRP is the matter of discussion under **"INTERPRETATION",** while HbA1c occupies the mind of **"TROUBLE SHOOTNG"** in this issue.

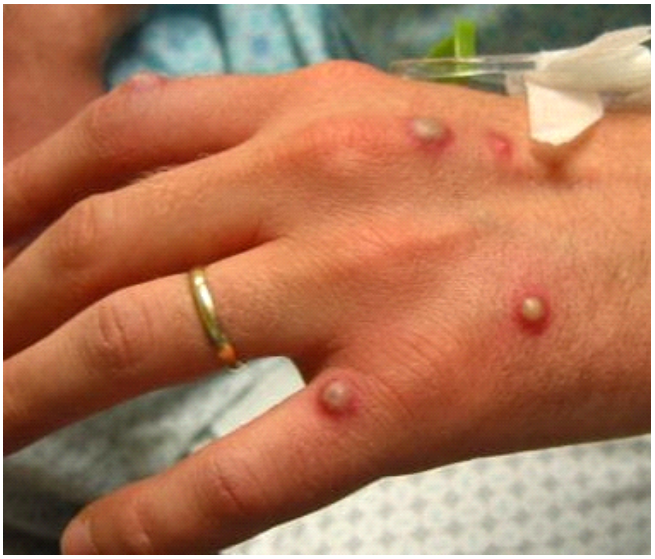
Little fun hasn't been overlooked. Take peep/ flip over.

DISEASE DIAGNOSIS

MONKEY POX

Practice Essentials

In 1970, when smallpox was nearly eradicated, a previously unrecognized orthopoxvirus named monkeypox was identified in humans. The first known human case occurred in the Equateur province of Zaire (now known as the Democratic Republic of Congo [DRC]) when a 9-year-old boy developed a smallpoxlike illness, which was eventually confirmed as human monkeypox by the World Health Organization. Retrospectively, similar cases occurring in 1970-1971 from the Ivory Coast, Liberia, Nigeria, and Sierra Leone were attributed to monkeypox infection. Monkeypox was limited to the rain forests of central and western Africa until 2003, when the first cases in the Western Hemisphere were reported. In late spring 2003, multiple persons were identified in the midwestern United States who had developed fever, rash, respiratory symptoms, and lymphadenopathy following exposure to ill pet prairie dogs (*Cynomys* species) infected with the monkeypox virus. Most confirmed cases reported direct contact or exposure to ill prairie dogs showing signs of profuse nasal discharge, ocular discharge, dyspnea, lymphadenopathy, and mucocutaneous lesions. Traceback investigators concluded that all confirmed cases of monkeypox were associated from a common animal distributor where prairie dogs were housed or transported with African rodents from Ghana. Among these rodents were Gambian rats, which are known reservoirs of monkeypox in their native habitat of Africa. In the 2003 US outbreak, imported asymptomatic animals transmitted a nonindigenous pathogen to an indigenous susceptible animal. After an average incubation period of 12 days, the animal became ill and was capable of transmitting the pathogen to humans when in close proximity. The exact potential for human-to-human transmission and human-to-animal transmission remains unknown. Note the image below.



Vesicular rash on the dorsal aspect of the hand. Vesicopustules are seen; some have a central umbilication.

In July 2021, a case of monkeypox was reported in Dallas, Texas in a traveler from Nigeria. Later, in November of that year, a second US case was confirmed in Maryland in another traveler returning from Nigeria. These 2 cases represent the only reported incidents of monkeypox in the US during 2021. In early May 2022, the United Kingdom reported 9 cases of monkeypox, with the first identified case having recently traveled to Nigeria. From this adult index case, there were 2 confirmed transmissions within the patient's family, to another adult and a toddler. On May 18, 2022, the Massachusetts Department of Public Health announced a confirmed case of monkeypox in an adult male who had recently visited Canada. This current outbreak continues to evolve rapidly. There have been no deaths from monkeypox during the current outbreak thus far. As of June 10, 2022, there were over 1500 total confirmed monkeypox cases outside of non-endemic countries among the following nations:

- Argentina
- Australia
- Austria
- Belgium
- Brazil
- Canada
- Czech Republic
- Denmark
- Finland
- France
- Germany
- Gibraltar
- Greece
- Hungary
- Iceland
- Ireland
- Israel
- Italy
- Latvia
- Malta
- Mexico
- Morocco
- Netherlands
- Poland
- Portugal
- Slovenia
- Spain
- Sweden
- Switzerland
- United Arab Emirates
- United Kingdom
- United States

Additionally, there was at least 1 case of monkeypox in each of the following US states:

- Arizona
- California
- Colorado
- District of Columbia (Washington, DC)
- Florida
- Georgia
- Hawaii
- Illinois
- Massachusetts
- New York state
- Oklahoma
- Pennsylvania
- Rhode Island
- Texas
- Utah
- Virginia
- Washington state

Many of the current cases are among men who have sex with men. While monkeypox is not believed to be sexually transmitted, the virus can be spread by droplets and direct contact with lesions.

Etiology

Outbreaks in western and central Africa have been linked to exposure to rats, rabbits, squirrels, monkeys, porcupines, and gazelles. Inhabitants of remote tropical rain forests may become infected from direct contact while capturing, slaughtering, and/or preparing these animals for food; ingestion has also been linked to infection. Consumption of such so-called "bush meat" is particularly hazardous because the flesh is often undercooked. Because of the diversity of animals eaten by local inhabitants, conclusions about the relative risk of meat sources are not known with certainty.

Prognosis

Mortality rates ranging from 1-10% have been reported in Africa, but no fatalities occurred in the United States 2003 outbreak.

History and physical examination

Monkeypox can cause a syndrome clinically similar to smallpox but

overall is less infectious and less deadly. Transmission can occur from contact with ill animals or animal reservoirs from Western Africa (eg, prairie dogs, rabbits, rats, mice, squirrels, dormice, monkeys, porcupines, gazelles). Additionally, preparing or ingesting infected animals can transmit monkeypox infection. Finally, direct cutaneous (skin-to-skin) or respiratory contact with an animal or person who is infected can transmit the infection. The incubation period averages 12 days, ranging from 4-20 days. In the prodrome or preeruptive stage (lasts 1-10 d), fever is commonly the first symptom (usually 38.5-40.5°C). The febrile illness is often accompanied by chills, drenching sweats, severe headache, backache, myalgia, malaise, anorexia, prostration, pharyngitis, shortness of breath, and cough (with or without sputum). Lymphadenopathy appears within 2-3 days after the fever. In the 2003 outbreak, 47% of patients had nodes measuring several centimeters in diameter in the cervical and submental areas. In the exanthem (eruptive) stage, most persons develop a rash within 1-10 days after the onset of fever. The rash often starts on the face and then spreads to the rest of the body. It persists for 2-4 weeks until all lesions have shed the crusts. Encephalitis with immunoglobulin M found in the cerebrospinal fluid has been reported. The most reliable clinical sign differentiating monkeypox from smallpox and chickenpox is enlarged lymph nodes, especially the submental, submandibular, cervical, and inguinal nodes.

Complications

Complications include pitted scars, deforming scars, secondary bacterial infection, bronchopneumonia, respiratory distress, keratitis, corneal ulceration, blindness, septicemia, and encephalitis.

Diagnostics

Refer to the information established by the US Centers for Disease Control and Prevention (CDC) at Monkeypox: Clinical Recognition.
Also see Workup.

Treatment

The disease is usually self-limited; resolution occurs in 2-4 weeks. In the African cases, the mortality rate was 1-10%, and death was related to the patients' health status and other comorbidities. Most patients died of secondary infections. No fatalities were reported in the 2003 US outbreak. Patients often feel poorly during the febrile stage of the illness; therefore, bedrest along with supportive care may be necessary. Hospitalization may be necessary in more severe cases; a negative pressure room is preferable.

In September 2019, the US Food and Drug Administration (FDA) approved an attenuated, live, nonreplicating smallpox and monkeypox vaccine (Jynneos) for immunization of adults at high risk for smallpox or monkeypox infection.

Pathophysiology

The monkeypox virus is a member of the genus orthopox (family Poxviridae); other members include cowpox, vaccinia, and variola (smallpox) viruses. It is a zoonotic virus with primary transmission believed to occur through direct contact with infected animals or possibly by ingestion of their inadequately cooked flesh. Inoculation may be from cutaneous or mucosal lesions on the animal, especially when the skin barrier is compromised secondary to bites, scratches, or other trauma. The infection was first seen in laboratory monkeys in 1958, thus, the name monkeypox, although rodents are believed to be the major reservoir in Africa. A 2010 study reaffirmed that several species of forest-dwelling rodents are at risk for orthopoxvirus (including monkeypox) infection. People living in or near the forested areas may have indirect or low-level exposure, possibly leading to subclinical infection. Secondary, or human-to-human, disease transmission was found to be another possible route in an outbreak in the DRC in 1996-1997. Studies of this outbreak suggested that within households, monkeypox was secondarily transmitted to 8-15% of human contacts. Prior to this, monkeypox was not identified as an important worldwide health problem because human infection rates were not known to play a significant role in the pathogenesis. Analysis of the 2003 US outbreak implicates animal-to-animal and animal-to-human transmission as the significant route of transmission. However, in the 2003 US outbreak, clear exposure to an infected animal could not be identified in 1 case, and, therefore, human-to-human transmission could not be excluded. Human-to-human transmission has been confirmed as a major factor in the 2022 outbreak in multiple areas across the world. While many of the patients are men who have sex with men, sexual transmission of monkeypox has not been confirmed.

Etiology

In the DRC in 1997, animals caught from the wild were tested for the monkeypox virus. The following animals were found to have neutralizing antibodies against the monkeypox virus, suggesting a role as natural reservoirs: domestic pig (*Sus scrofa*), Gambian rat (*Cricetomys emini*), elephant shrew (*Petrodromus tetradactylus*), Thomas's tree/rope squirrel (*Funisciurus anerythrus*), Kuhl's tree squirrel (*Funisciurus congicus*), and sun squirrel (*Heliosciurus rufobrachium*). Human-to-human transmission supplanted the prominence of animal-to-human transmission in the 1996-1997 outbreak in the DRC. Crowded living quarters, poor hygiene, discontinuation of the smallpox vaccination, and decreased herd immunity were implicated. Respiratory droplets and direct contact with mucocutaneous lesions or fomites have been postulated as routes of human-to-human transmission.

Epidemiology

Frequency

United States

No cases occurred in the United States until the late spring 2003 outbreak in the Midwestern states. Between May 16 and June 20, 2003, 71 suspected cases of monkeypox were investigated. A total of 47 individuals were identified with confirmed (n = 37) or probable (n = 10) monkeypox virus infection. Monkeypox cases were confirmed on the basis of virus isolation or detection of the virus by polymerase chain reaction (PCR) from a clinical specimen (eg, skin biopsy or throat culture). Individuals who presented with fever and rash within 21 days of exposure to monkeypox and had serum positive for orthopox immunoglobulin M (IgM), but did not have culture- or PCR-positive clinical specimens, were classified as having a probable case of infection. Two cases were confirmed in the US during 2021. As of May 18 there had been a single confirmed US case, in Massachusetts, during 2022.

International

This condition is rare and only known to be indigenous to the rain forests of western and central Africa. It was first recognized in humans in 1970 after the eradication of smallpox, possibly because of the subsequent unmasking of the infection. Surveillance reports from 1981-1986 documented 338 cases in the DRC (out of a 1982 estimated population of 5 million). In the 1996-1997 outbreak in the DRC, the attack rate was 22 cases per 1000 population. Human infection with monkeypox has not been reported in West Africa since 1978. Monkeypox is considered

endemic in northern and central DRC. Sporadic occurrences of disease are reported in neighboring countries. In 2003, 11 cases and 1 death were reported from the DRC and 10 cases with no deaths were reported from Sudan in 2005. In 2009, interethnic violence in northwestern DRC lead to an influx of refugees into the Republic of the Congo (ROC). The United Nations International Children's Emergency Fund (UNICEF) sponsored a program of intensive community education in the refugee settlements that included modules on monkeypox recognition and prevention, which resulted in the indentification of 10 suspected cases of monkeypox. Seven of these 10 cases were tested and 2 were found to be positive by polymerase chain reaction assays. The results of this outreach campaign suggest that intensive community education can lead to increased capacity for detection of monkeypox in high transmission–risk settings. They also highlight the need to educate physicians in the recognition and treatment of monkeypox.

Race, sex, and age

Poxvirus infections have no racial predilection, and the incidence is equal in males and females. In the African epidemics, 90% of the patients were children younger than 15 years. In the 2003 US outbreak, of the confirmed cases (n = 35), 11 patients were younger than 18 years and 24 were older. Although the highest age-specific incidences and the greatest number of cases occur among persons younger than 15 years, a trend toward increasing incidence among persons aged 15-30 years has been seen in recent years. It has been hypothesized that cessation of smallpox vaccination may be a factor in the increasing incidence in this age group, but this theory fails to account for why the disease has not reemerged in countries where the disease was seen previously, such as West Africa.

Prognosis

Mortality rates ranging from 1-10% have been reported in Africa, but no fatalities occurred in the United States 2003 outbreak. Death rates are disproportionately high in African children. Health status, comorbidities, vaccination status, and severity of complications influence the prognosis in the United States and Africa. Uncomplicated cases resolve in 2-4 weeks, with only pock scars remaining.

Mortality/morbidity

The disease in the United States was generally self-limited, with resolution in 2-4 weeks, depending on the severity of the illness. However, a small subset of patients, most commonly pediatric patients, had a more severe course, with several patients requiring ICU care. Complications reported from African outbreaks include pitted scars, deforming scars, secondary bacterial infection, bronchopneumonia, respiratory distress, keratitis, corneal ulceration, blindness, septicemia, and encephalitis. Data from the African outbreaks suggest that prior smallpox vaccination confers 85% protection from monkeypox; infection may be milder even several years after vaccination, and the incidence of complications may be reduced. With the 2003 US outbreak, the Centers for Disease Control and Prevention (CDC) recommended smallpox vaccination up to 2 weeks, ideally within 4 days, after a significant, unprotected exposure to a diseased animal or a confirmed human case.

African cases have mortality rates of 1-10%, with the highest rates occurring in children and individuals without vaccination. In general, the prognosis is related to the amount of exposure to the virus, host immune response, comorbidities, vaccination status, and severity of complications. Genomic sequencing of US, western African, and central African monkeypox isolates have confirmed the existence of 2 distinct monkeypox clades. The isolates from the United States were identical to the western African isolates. The disease course for individuals infected with the western African isolates is milder with less human-to-human transmission than for those infected with isolates from central Africa. In 2010, a dosage comparison using a prairie dog animal model reconfirmed that the Congo Basin strain of monkeypox virus is more virulent than the West African strain of monkeypox virus.

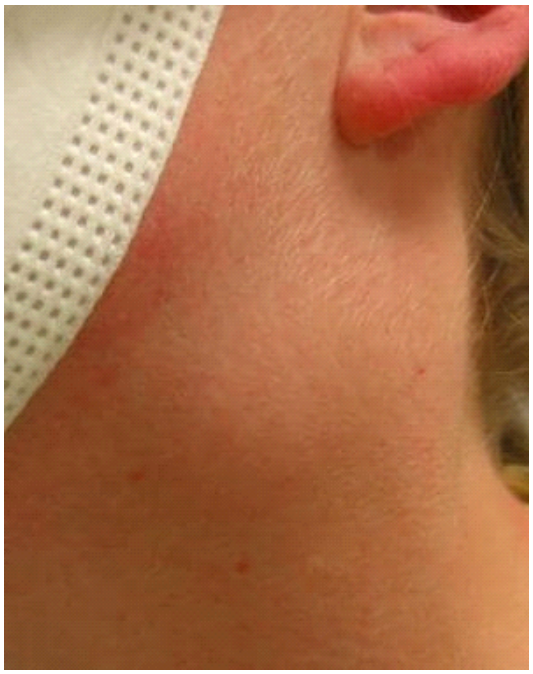
Patient Education

After the 2003 outbreak, the CDC implemented an immediate embargo on the importation of all rodents (order Rodentia) from Africa. In addition, the Centers for Disease Control and Prevention (CDC) and the US Food and Drug Administration (FDA) prohibited the transportation or offering for transportation in interstate commerce, or the sale, offering for sale, or offering for any other type of commercial or public distribution, including release into the environment of prairie dogs and the following rodents from Africa: tree squirrels (*Heliosciurus* species), rope squirrels (*Funisciurus* species), dormice (*Graphiurus* species), Gambian giant pouched rats (*Cricetomys* species), brush-tailed porcupines (*Atherurus* species), and striped mice (*Hybomys* species). Investigation of the exotic pet industry by state and federal authorities was triggered by the 2003 outbreak. The FDA lifted its restrictions on pet prairie dogs in 2008. The FDA consulted with the CDC and determined that the domestic restrictions placed on certain African rodents, prairie dogs, and certain other animals were no longer needed. However, the CDC restriction on the importation of all African rodents remains in effect to prevent any reintroduction of the monkeypox virus into the United States.

Clinical Presentation

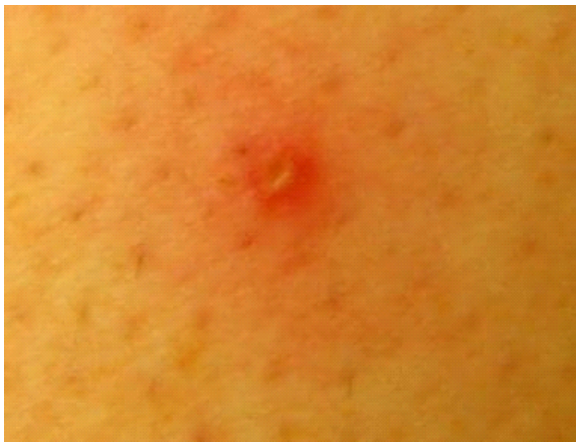
Physical Examination

The most reliable clinical sign differentiating monkeypox from smallpox and chickenpox is enlarged lymph nodes, especially the submental, submandibular, cervical, and inguinal nodes. Note the image below.



Lymphadenopathy in monkeypox. Large nodes in the mandibular, cervical, or inguinal region are commonly seen in monkeypox. The presence of significant lymphadenopathy helps differentiate monkeypox from smallpox and chickenpox. With regard to enanthema, nonspecific lesions and inflammation of the pharyngeal, conjunctival, and genital mucosae have been observed. In the exanthema stage, within a particular body region, lesions evolve synchronously over 14-21 days,

similar to the development of lesions with smallpox. However, unlike smallpox, skin lesions may appear in crops. In contrast to smallpox, the lesions do not have a strong centrifugal distribution. Lesions progress from macules to papules to vesicles and pustules; umbilication, crusting, and desquamation follow. Most lesions are 3-15 mm in diameter.
Note the image below.



Umbilicated papule on the lower part of the leg. This smaller lesion still shows the typical umbilicated morphology.

The face, the trunk, the extremities, and the scalp are involved. Lesions appear in covered and uncovered areas. Lesions may be seen on the palms and the soles. Necrosis, petechiae, and ulceration may be features. Pain is unusual, and, if it occurs, it is often associated with secondary bacterial infection. Pruritus may occur. In patients who have been previously vaccinated against smallpox, a milder form of disease occurs. In children, the lesions may appear as nonspecific, erythematous papules that are 1-5 mm in diameter and suggestive of arthropod bite reactions. Subtle umbilication may be seen. In the African outbreaks, 20% of unvaccinated patients developed a confluent, erythematous eruption on the face and the upper part of the trunk, which some authors have termed the septicemic rash of monkeypox. Hemorrhagic and flat forms, which can be seen with smallpox, have not been reported in patients with monkeypox. Deep pock scars can result as the lesions resolve. During the 2022 outbreak, a significant number of patients with monkeypox are men who have sex with men. In several case, the perianal and genital areas have been reported as the first sites of lesion appearance. Clinicians should have a high suspicion for monkeypox with the identification of characteristic lesions in these areas, particularly if the patient has a history of recent travel.

Differential Diagnoses

- Smallpox

Diagnostic Criteria

Meets 1 or more of the following laboratory criteria:

- Isolation of the monkeypox virus in culture from a sample obtained from the patient
- Demonstration of the monkeypox virus on PCR in a specimen obtained from the patient
- Demonstration of the orthopox virus by electron microscopy in samples obtained from the patient in the absence of exposure to other orthopoxviruses
- Demonstration of the monkeypox virus by immunohistochemical methods in samples obtained from the patient in the absence of exposure to another orthopoxvirus

Probable case

This is contact that meets current epidemiologic criteria per the CDC. It is the occurrence of fever and vesicular-pustular rash, with the onset of the first sign or symptom at most 21 days after the last exposure, meeting the epidemiologic exposure.

Suspected case

This is contact that meets current epidemiologic criteria per the CDC. It the occurrence of fever or unexplained rash and 2 or more other signs or symptoms, with the onset of the first sign or symptom at most 21 days after exposure, meeting the epidemiologic criteria. Symptoms are as follows:

- Chills and/or sweats
- Sore throat
- Shortness of breath
- Backache
- Lymphadenopathy
- Cough
- Headache

Laboratory Studies

Information regarding procurement and disposition of specimens for the CDC may be obtained at Laboratory Testing of Human and Animal Specimens. A viral culture should be obtained from an oropharyngeal or nasopharyngeal swab. A skin biopsy specimen of the vesiculopustular rash or a sample of the roof of an intact vesiculopustule should be analyzed. Tissue for PCR of DNA sequence-specific for the monkeypox virus may be obtained. Paired sera for acute and convalescent titers may be analyzed. Serum collected more than 5 days for IgM detection or serum collected more than 8 days after rash onset for IgG detection was most efficient for the detection of the monkeypox virus infection. A Tzanck smear can help differentiate monkeypox from other nonviral disorders in the differential diagnosis. However, a Tzanck smear does not differentiate a monkeypox infection from smallpox or herpetic infections. A pilot of the Tetracore Orthopox BioThreat Alert provided promising results using lesion specimens from acute Orthopoxvirus infections. This assay correctly identified 5 of 6 clinical specimens tested. Although not specific for monkeypox virus, this assay could be used in monkeypox-endemic areas for Orthopoxvirus confirmation by proxy.

Histologic Findings

Histologically, papular lesions show acanthosis, individual keratinocyte necrosis, and basal vacuolization. This is accompanied by a superficial and deep perivascular, lymphohistiocytic infiltrate in the dermis. Lesions in the vesicular stage demonstrate spongiosis with reticular and ballooning degeneration. Multinucleated epithelial giant cells may be seen. Pustular lesions are characterized by epidermal necrosis with numerous eosinophils and neutrophils, many displaying karyorrhexis. Necrosis may extend through full-thickness epidermis with sharp lateral demarcation from adjacent intact epidermis. The associated perivascular infiltrate includes eosinophils and neutrophils in addition to lymphocytes and histiocytes. Petechial lesions demonstrate secondary vasculitis. Amphophilic intranuclear structures suggestive of viral inclusions may be seen in keratinocytes. Immunohistochemistry staining for orthopox viral antigens can be performed in a reference laboratory. With electron microscopy, intracytoplasmic, round-to-oval inclusions with sausage-shaped structures centrally, measuring 200-300 µm, are observed. Inclusions are consistent with orthopox viruses, permitting differentiation from parapox and herpes viruses.

Treatment & Management

Medical Care

The disease is usually self-limited; resolution occurs in 2-4 weeks. In the

African cases, the mortality rate was 1-10%, and death was related to the patients' health status and other comorbidities. Most patients died of secondary infections. No fatalities were reported in the 2003 US outbreak. Patients often feel poorly during the febrile stage of the illness; therefore, bedrest along with supportive care may be necessary. Hospitalization may be necessary in more severe cases; a negative pressure room is preferable. To avoid infection of health care workers and close contacts, airborne and contact precautions should be applied. See the current CDC recommendations at Infection Prevention and Control of Monkeypox in Healthcare Settings. Isolation must be continued until the last crust is shed.

Prevention

Importation of exotic animals as domestic pets poses a threat to the health of both people and animals by introducing nonindigenous pathogens. Animals, especially those implicated above (see Causes) or those in contact with them, demonstrating signs of respiratory distress, mucocutaneous lesions, rhinorrhea, ocular discharge, and/or lymphadenopathy should be quarantined immediately. Avoidance of contact, especially bites, scratches, and exposure to fluids/secretions, is essential. Guidance can be obtained from veterinarians, state/local authorities, and the CDC. See the current CDC recommendations at Monkeypox Infections In Animals: Updated Interim Guidance for Veterinarians. In September 2019, the FDA approved an attenuated, live, nonreplicating smallpox and monkeypox vaccine (Jynneos) for immunization of adults at high risk for smallpox or monkeypox infection. Approval was determined in a clinical study comparing the immune responses in study participants who received either Jynneos or ACAM2000, an FDA-approved vaccine for the prevention of smallpox. The study included approximately 400 healthy adults, aged 18-42 years who had never been vaccinated for smallpox. Half of the study participants received 2 doses of Jynneos administered 28 days apart, and half received 1 dose of ACAM2000. The group vaccinated with Jynneos had an immune response that was not inferior to immune responses to ACAM2000. A 2010 report describes experimental low-dose intranasal infection in a STAT1-deficient C57BL/6 mouse model that caused 100% mortality. However, vaccination with modified vaccinia virus Ankara, followed by a booster vaccination, was protective against intranasal infection and produced a more vigorous immune response compared with a single vaccination. Other mouse models are being used to investigate monkeypox pathogenesis, disease progression, viral shedding, and virulence, with the possible aim of testing antivirals and next-generation vaccines.

Long-Term Monitoring

Outpatient management is appropriate and cost-effective in most cases of human infection, but care must be taken to follow recommended quarantine procedures at home. Contact and respiratory isolation precautions should be exercised to prevent the spread of disease. Direct contact with skin lesions or fomites is considered infectious until the crust detaches from the last skin lesion. Patients and unexposed contacts should wear masks until respiratory symptoms resolve. Health care workers and others who are asymptomatic and in contact with patients who are infected must closely monitor their symptoms and their temperature for 21 days after the last known contact. See the current CDC recommendations at Infection Prevention and Control of Monkeypox in Healthcare Settings.

Medication Summary

The CDC recommends a smallpox or smallpox/monkeypox vaccination within 2 weeks of exposure, ideally within 4 days, for exposed health care workers and household contacts of confirmed cases. Antiviral agents (ie, tecovirimat, brincidofovir, cidofovir) are possible treatment options in severe, life-threatening cases. These agents may be used under an expanded access investigational new drug (EA-IND) available from the CDC. Additionally, vaccinia immune globulin (VIG) may be considered, but has not demonstrated efficacy as either treatment or prophylaxis. Smallpox preparedness research has led to the development of new antiviral agents for the treatment of orthopoxvirus infections. In September 2019, the FDA approved an attenuated, live, nonreplicating smallpox and monkeypox vaccine (Jynneos) for immunization of adults at high risk for smallpox or monkeypox infection.

Vaccine, Live Virus

Class Summary

Vaccinia vaccine promotes active immunity against the smallpox virus by inducing specific antibodies. Currently available stocks of vaccinia vaccine were derived from the vaccinia strain maintained at the New York Board of Health. Wyeth Laboratories manufactured the last batches of the vaccine (Dryvax) in the early 1980s. These batches were made by using the calf lymph method, and they were lyophilized but are no longer available. Several attenuated vaccinia vaccine candidates are undergoing investigation, with ACAM2000 receiving FDA approval as a replacement for Dryvax. Another vaccine (smallpox [vaccinia] and monkeypox vaccine, live, nonreplicating [Jynneos]) has also been approved by the FDA for immunization of adults at high risk for smallpox or monkeypox infection. New, cell-derived lots of vaccinia appear to have adverse effect profiles similar to the older, calf lymph–derived lots. Primary immunization as soon as possible after exposure or at the first sign of infection is indicated for the prevention and management of smallpox. Currently, US military personnel, US Department of Defense civilian employees, and health care professionals are recommended candidates to receive the vaccination because they will likely be at highest risk in case of a biologic attack (eg, bioterrorism).

Smallpox vaccine (ACAM2000)

This agent is made from vaccinia, which is related to, but different from, the virus that causes smallpox. It contains live vaccinia virus and works by causing a mild infection that stimulates an immune response that effectively protects against smallpox without actually causing disease. The vaccine contains live vaccinia virus but does not contain variola virus, the virus that causes smallpox. Vaccinia is a member of the Orthopoxvirus genus, which includes smallpox (variola), cowpox, monkeypox, gerbilpox, camelpox, and others. Following inoculation, the vaccine induces an immune reaction that serves to protect against smallpox. The medication guide explains proper care of the vaccination site and provides information about serious adverse effects associated with ACAM2000. In studies, about 1 in 175 healthy adults who received smallpox vaccine for the first time developed myocarditis and/or pericarditis. Of the 10 affected adults, 4 had no symptoms at the end of the study, and symptoms resolved in all but 1 patient.

Smallpox (vaccinia) and monkeypox vaccine, live, nonreplicating (Jynneos)

This vaccine is derived from a vaccinia virus, a virus that is closely related to, but less harmful than, variola and monkeypox viruses and can protect against both of these diseases. It is indicated for prevention of smallpox and monkeypox disease in adults who are at high risk for smallpox or monkeypox infection. It is administered as a 2-dose series administered 4 weeks apart.

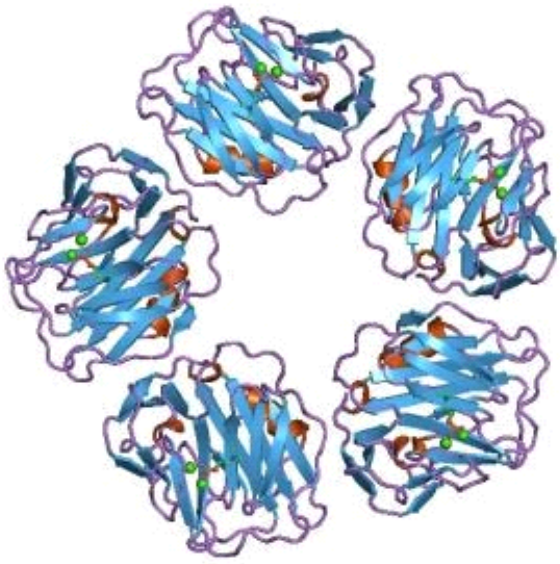
INTERPRETATION

CRP

Background

Description

CRP -- an acute phase serum protein – is a surrogate for the pro-inflammatory interleukin IL-6. It is a member of pentraxin family of proteins and is synthesized by liver. CRP is also produced by cells in the vascular wall such as endothelial cells, smooth muscle cells, and also by adipose tissue. It was discovered by Tillett and Francis in 1930. CRP is a 224-residue protein with a molecular weight of 25106 Da. The CRP gene is located on chromosome 1. CRP was so named because of its capacity to precipitate the somatic C-polysaccharide of Streptococcus pneumonia. It has no relationship with protein C or C-peptide. It activates the complement system and binds to Fc receptors. Significant rise in CRP indicates clinically relevant inflammation, and in contrast, the absence of a high CRP helps in exclusion of infection/inflammation. Sequential CRP may provide a more accurate assessment of inflammatory changes in response to treatment. CRP is very helpful in assigning a non-inflammatory cause to a markedly abnormal ESR. As for instance, in a patient with a monoclonal protein without any evidence of infection, ESR may be high (in 100) but CRP will be normal. One should be cautious about the interpretation of CRP levels. CRP changes with body mass index. The new ultrasensitive CRP assays expressed in markedly different concentrations may be very confusing to the unwary. An image depicting C-reactive protein can be seen below.



C-reactive protein, pentraxin-related.

Chronic inflammation is pivotal in heart disease; studies have shown that high levels of CRP, measured by hs-CRP, can be a marker of atherosclerosis. hs-CRP is an important predictor for cardiovascular events, including myocardial infarction, cerebrovascular events, peripheral vascular disease, and sudden cardiac death in individuals without a history of heart disease. In patients with acute coronary disease, CRP level predicts mortality and cardiac complications. High CRP levels augur a worse prognosis in patients with acute coronary syndromes. hs-CRP is also a marker of metabolic syndrome.

Indications/Applications

- CRP - Suspected inflammatory state (vasculitis, autoimmune disorders, SLE, psoriasis, infection)
- CRP may sometimes be ordered along with erythrocyte sedimentation rate (ESR)
- CRP may be ordered, for example, when a newborn shows signs of infection or when an individual has symptoms of sepsis, such as fever, chills, and rapid breathing and heart rate
- CRP may also be ordered to monitor conditions such as rheumatoid arthritis and lupus and is often repeated at intervals to determine effectiveness of treatment
- hs-CRP can be ordered for patients with some established risk factors of coronary heart disease to determine strategy for prevention of cardiovascular events and for follow-up of patients with acute coronary syndromes

Considerations

CRP, being a marker of acute inflammation, is elevated 100-1000 fold after infection or trauma and, thus, for its utility as a cardiovascular risk marker, it needs to be measured 2 times at least 2 weeks apart, in a metabolically stable state, post-infection or illness, since its half-life is 19 days. Universal hs-CRP screening is currently not warranted except in patients with an intermediate-high Framingham risk score. The median baseline level of CRP for young adults is 0.8 mg/L (the 90th percentile is 3.0 mg/L, and the 99th percentile is 10 mg/L). However, CRP levels may increase from less than 50 µg/L to more than 500 mg/L, that is, 10,000-fold, following an acute-phase reaction. The baseline CRP increases with age and with body mass index. Some laboratories provide a choice for a routine CRP assay (suitable for the detection and monitoring of inflammatory disease) versus a highly sensitive CRP assay for the determination of cardiac risk. CRP level is useful both in the clinical assessment of chronic inflammatory disorders and assessment of vascular inflammation, and therefore, in cardiovascular risk stratification. CRP level has been found to be an independent risk factor for atherosclerotic disease. In patients with coronary artery disease, high CRP level is associated with increased cardiovascular morbidity and mortality. High sensitivity CRP (hsCRP), a marker of systemic inflammation, has been identified as a valid biomarker of cardiovascular risk. The best evidence to date supports the use of hs-CRP as an independent predictor of high risk for coronary artery disease. The cut points of low risk (< 1.0 mg/L), average risk (1.0 to 3.0 mg/L), and high risk (>3.0 mg/L) correspond to approximate tertiles of hs-CRP in the adult population. The low-risk tertile has about half in relative risk compared with the high-risk tertile. CRP rises rapidly reaching a peak in 2 days during an acute phase reaction. CRP decreases rapidly with the resolution of the acute phase response (with a half-life of 18 hours). High CRP level does not have diagnostic specificity, as a large number of clinical conditions increase CRP. A high CRP lends support for suspected inflammatory disease, such as giant cell arteritis or polymyalgia rheumatica, when other features are sparse or absent. CRP more than 10 mg/L indicates clinically significant inflammation. Therefore, monitoring CRP levels may provide useful information on the diseases activity such as flare up of rheumatoid arthritis and giant cell arteritis. However, elevations of CRP may occur in renal failure even without clinically significant inflammation. CRP usually does not increase (may be a slight rise) in scleroderma, polymyositis, and dermatomyositis. CRP levels also tend not to be elevated in SLE unless serositis or synovitis is present.

Reference Range

The normal finding for C-reactive protein (CRP) is < 1.0 mg/dL or < 10.0 mg/L (SI units) (< 3 mg/L for high-sensitivity CRP [hs-CRP]).
Cardiac risks associated with C-reactive protein levels are as follows :

- Low: < 1.0 mg/dL
- Average: 1.0-3.0 mg/dL
- High: >3.0 mg/dL

Interpretation

Hs-CRP appears within 1-2 days of acute myocardial infarction, peaks at 3 days, and becomes negative after 7 days. Failure of CRP to return to normal signifies tissue damage in the cardiac or other tissues. The absence of a CRP increase raises the question of necrosis in prior to 2 to 10 days. CRP does not usually increase in patients with unstable angina. Hs-CRP correlates with peak creatine kinase-MB (CK-MB) following acute myocardial infarction. CRP may remain high for at least three months following acute myocardial infarction.

Increased in

Acute or chronic inflammatory conditions
Tissue necrosis or tissue injury
Ischemia or infarction of issues
Infection, inflammation
Metabolic syndrome
Malignant tumors especially of breast, lung and gastrointestinal tract
Acute pancreatitis
Post-surgery
Burn
Leukemia
Tobacco smoking
Hormone replacement therapy
Obesity

In a report on older Black adults (aged 51 years or older), Farmer et al found elevated CRP in more than half of the study group's women, with the increase indicated to have links to such factors as younger age, Medicaid, religiosity, overweight/obesity, physical inactivity, and activities of daily living (ADLs). A lower incidence of elevated CRP (37.25%) was found among Black men, with religiosity, reduced neighborhood cohesion, current smoking, overweight/obesity, ADLs, and more chronic conditions being associated with these higher levels. Moreover, among men, financial distress was linked to a decreased risk for high CRP.

Decreased in

Exercise, weight loss, moderate alcohol consumption, medications like statins, niacin and fibrates

Limitation

Sex and race affect the CRP levels. African Americans have higher level than Caucasians and women have higher values than men.

TROUBLESHOOTING

Hemoglobin A1C (HbA1c) Test

What is a hemoglobin A1c (HbA1c) test?

A hemoglobin A1c (HbA1c) test measures the amount of blood sugar (glucose) attached to hemoglobin. Hemoglobin is the part of your red blood cells that carries oxygen from your lungs to the rest of your body. An HbA1c test shows what the average amount of glucose attached to hemoglobin has been over the past three months. It's a three-month average because that's typically how long a red blood cell lives. If your HbA1c levels are high, it may be a sign of diabetes, a chronic condition that can cause serious health problems, including heart disease, kidney disease, and nerve damage. Other names: HbA1c, A1c, glycohemoglobin, glycated hemoglobin, glycosylated hemoglobin.

What is it used for?

An HbA1c test may be used to check for diabetes or prediabetes in adults. Prediabetes means your blood sugar levels show you are at risk for getting diabetes. If you already have diabetes, an HbA1c test can help monitor your condition and glucose levels.

Why do I need an HbA1c test?

The Centers for Disease Control (CDC) recommends that adults over the age of 45 get tested to screen for diabetes and prediabetes. If your results are normal, you should repeat the test every 3 years. If your results show you have prediabetes, you should get tested every 1-2 years. You should also talk to your health care provider about taking steps to reduce your risk of developing diabetes. If you are under 45, you may need this test if you have certain risk factors. These include:

- Being overweight or obese
- High blood pressure
- History of heart disease
- Physical inactivity

Testing should be done every 3 years, and more frequently if your results show you have prediabetes.

You may also need an HbA1c test if you have symptoms of diabetes. These include:

- Increased thirst
- Increased urination
- Blurred vision
- Fatigue

What happens during an HbA1c test?

A health care professional will take a blood sample from a vein in your arm, using a small needle. After the needle is inserted, a small amount of blood will be collected into a test tube or vial. You may feel a little sting when the needle goes in or out. This usually takes less than five minutes.

Will I need to do anything to prepare for the test?

You don't need any special preparations for an HbA1c test.

Are there any risks to the test?

There is very little risk to having a blood test. You may have slight pain or bruising at the spot where the needle was put in, but most symptoms go away quickly.

What do the results mean?

HbA1c results are given in percentages. Typical results are below.

- **Normal**: HbA1c below 5.7%
- **Prediabetes**: HbA1c between 5.7% and 6.4%
- **Diabetes**: HbA1c of 6.5% or higher

Your results may mean something different. If you have questions about your results, talk to your health care provider. If you have diabetes, the American Diabetes Association recommends keeping your HbA1c levels below 7%. Your health care provider may have other recommendations for you, depending on your overall health, age, weight, and other factors.

Is there anything else I need to know about an HbA1c test?

The HbA1c test is not used for gestational diabetes, a type of diabetes that only affects pregnant women, or for diagnosing diabetes in children. Also, if you have anemia or another type of blood disorder, an HbA1c test may be less accurate for diagnosing diabetes. If you have one of these disorders and are at risk for diabetes, your health care provider may recommend different tests.

DIAGNOSTIC TESTS

HbA1c Test for Diabetes- Other Considerations

HbA1c is an important blood test that gives a good indication of how well your diabetes is being controlled. Together with the fasting plasma glucose test, the HbA1c test is one of the main ways in which type 2 diabetes is diagnosed. HbA1c tests are not the primary The HbA1c test, also known as the haemoglobin A1c or glycated haemoglobin test, diagnostic test for type 1 diabetes but may sometimes be used together with other tests.

The **World Health Organisation (WHO**) suggests the following diagnostic guidelines for diabetes:

- **HbA1c below 42 mmol/mol (6.0%):** Non-diabetic
- **HbA1c between 42 and 47 mmol/mol (6.0–6.4%):** Impaired glucose regulation (IGR) or Prediabetes
- **HbA1c of 48 mmol/mol (6.5%) or over:** Type 2 diabetes

If your HbA1c test returns a reading of **6.0–6.4%,** that indicates prediabetes. Your doctor should work with you to suggest appropriate lifestyle changes that could reduce your risk of developing type 2 diabetes. HbA1c is **not** used to diagnose gestational diabetes in the UK. Instead, an oral glucose tolerance test is used. A random blood glucose test will usually be used to diagnose type 1 diabetes. However, in some cases, an HbA1c test may be used to support a diagnosis of type 1 diabetes.

Why is HbA1c important?

People with diabetes who **reduced their HbA1c by less than 1%** can **cut their risk of dying within 5 years by 50%** , according to Swedish research presented at the annual meeting of the European Association for the Study of Diabetes, Sept. 2012 (EASD).

How does the HBA1c test work?

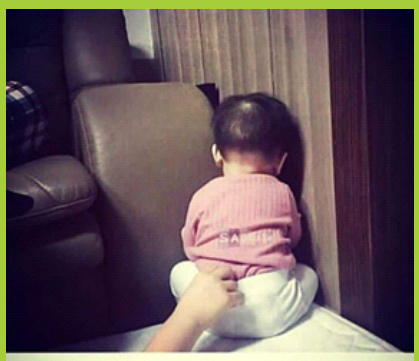
HbA1c (glycated haemoglobi, haemoglobin A1C) occurs when haemoglobi, the oxygen-carrying protein in red blood cells, becomes bonded with glucose in the bloodstream. The bonding with glucose is called glycation. The higher a person's blood glucose levels have been, the higher the number of red blood cells that will have become glycated, and therefore the higher HbA1c level they will have. Note that red blood cells exist in the body for around 3 months, therefore an HbA1c levels generally reflects a person's blood glucose levels over the previous 8-12 weeks.

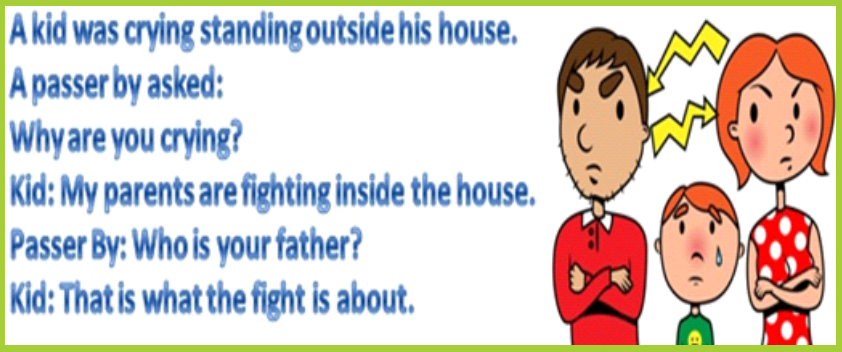
Limitations of HbA1c tests

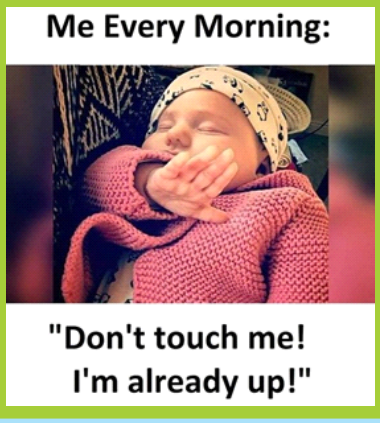
Whilst HbA1c tests are usually reliable, there are some limitations to the accuracy of the test. For example, people with forms of anaemia may not have sufficient haemoglobin for the test to be accurate and may need to have a fructosamine test instead. Being pregnant or having an uncommon form of haemoglobin (known as a haemoglobin variant) can also return an inaccurate HbA1c, while readings can also be affected by short term issues such as illness as they can cause a temporary rise in blood glucose. Because of the way the HbA1c test measures blood sugar, if you have higher blood sugar levels in the weeks leading up to your HbA1c test, this will have a greater impact on your test result than your glucose levels 2 to 3 months before the test.

BOUQUET

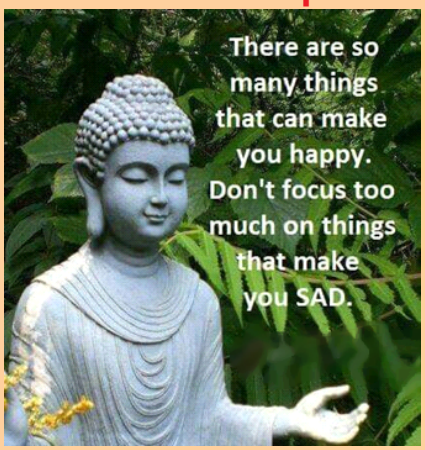
In Lighter Vein

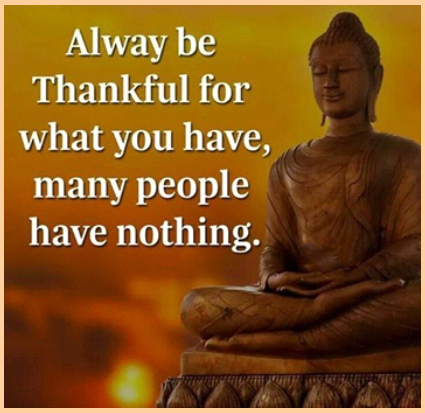






Wisdom Whispers





Brain Teasers

1. **How is Monkey pox spread**
   a. Through direct contact b. Air borne
   c. Sexual contact d. All of the above

2. **Causative organism of Monkey pox is a -----**
   a. Bacteria b. Fungi
   c. Virus d. Parasite

3. **This term is used to describe the bonding of a protein and sugar molecule.**
   a. Glutamizing b. Glycation
   c. Glutation d. Sugarization

4. **CRP can be used for these purposes**
   a. Assessment of the activity of inflammatory disease
   b. Used post-operatively to detect wound infections
   c. Management of neonatal septicemia and meningitis or effectiveness of the treatment
   d. All the above

ANSWER: 1: D, 2: C, 3: B, 4: D

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