Monkey Pox: Ignored or emerging pathogen

Karoll J. Cortez
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GBMC Medicine Grand Rounds
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Disclosures

• None
Clinical scenario

- 4 y/o previously healthy village child in Central Africa. Loves to play with farm animals in his backyard. His favorite is a small goat found dead a several days ago.
- Admitted to a tertiary center with a 3 days hx of low-grade temp (37.9°C), irritability, malaise, coryza (rhinitis, conjunctivitis and cough), R sided neck adenopathy, and a non-itchy maculo-papular rash over trunk and face and vesicular rash in his legs HR 115 bpm, RR 30
- No previous vaccinations
- No HIV testing done due to unavailability of antiretrovirals (testing for HIV was considered unethical and discouraged by medical project leader - Expatriate)
- 3 adults in the village had similar symptoms but milder.
CLASSIC CLINICAL FEATURES

SKIN LESIONS
McCollum AM and Damon IK. Clinical Infect Dis 2014, 58: 260-7

LYMPHADENOPATHIES
Differential Diagnosis?

* Measles
* Chickenpox
* Orf
* HIV
* Cryptococcosis
* Smallpox
* Monkeypox
* Cowpox
* Vaccinia
Case scenario (cont...)

-Hospital day 2 he was admitted to the isolation unit with his father on suspicion of measles or chickenpox. Blood sample sent to a diagnostic unit in the city of Kinshasa for IgM and IgG for measles.

-Hospital days 2-5 characterized to increased temp (39.2 C). Significant worsening of the skin lesions penetrating 2-3 mm into his skin simultaneously in addition to a painful stomatitis.

-Treatment with ceftriaxone and morphine started.

-His condition deteriorated with innumerable vesicles and pustules inability to eat or drink, fevers, encephalitis and the child passed away on hospital day 12. Serology came back negative for measles.
Case scenario (cont...)

* No additional samples were collected for further testing
* Local authorities recognized this case as Monkeypox.
* Supported by experts in pediatric infectious disease in Denmark who received photos and a case description via email.
* No contact tracing was undertaken.
This case effectively highlights the challenges in dealing with MP and opportunities to spot weakness in the management

* Lack of familiarity with the disease by treating physicians
* Lack of diagnostic tools in the rural setting
* Lack of access to information and guidelines to report, contact tracing, implementation of infection control measures, appropriate sample collection, handling and routing for diagnosing the disease and in severe cases access to appropriate life saving treatment.
MONKEYPOX

• Rare disease caused by Monkeypox virus

• A virus of the genus Orthopoxvirus that includes various viruses:
  • Variola virus (smallpox)
  • Vaccinia virus (used in the smallpox vaccine)
  • Cowpox virus

• Poxviridae family
POX virus under microscopy

Public Health Image Library #22663
MONKEYPOX

• First Discovered 1958

• Outbreak in Colonies of monkeys kept for research in Denmark “Monkeypox” coined

• First human case reported in 1970

• 9 months old infant in Democratic Republic of Congo (DRC) during efforts to eliminate smallpox
MONKEYPOX

* Outside Africa cases related to international travel or imported animals in the United States, United Kingdom, Israel, Singapore

* Natural reservoir: unknown

* African rodents and non-human primates may harbor the virus and infect people (Bush meat)

* Since 1970s Monkeypox has been reported in several other countries of central and western Africa majority of cases in Democratic Republic of Congo
Countries reporting human cases
Monkeypox

Human Monkeypox cases (1971–2019)
**Monkeypox:**

* Monkeypox is endemic in several African Countries
* Median age of presentation 4 (1070) to 21 (2010 – 2019)
* Overall fatality rate 8.7%
* Since 2003 import- and travel-related spread outside of Africa has occasionally resulted in outbreaks
* Interactions/activities with infected animals or individuals are risk behaviors associated with acquisition of Monkeypox
Monkeypox:

* This findings may be related with cessation of smallpox vaccination, which provided some cross-protection against Monkeypox.
* The appearance of outbreaks outside of Africa highlights the global relevance of the disease.
* Increased surveillance and detection of monkey pox cases are essential tools for understanding the continuously changing epidemiology of this resurging disease.
Monkeypox: situational update

As of May 2022

• Non-Endemic continent with cases: Europe, North America and Australia

• Most (not all cases) among men who have sex with men who identify as: gay, bisexual

• US CDC working with US states and other countries

• As of most recent CDC outreach in the USA
  • 8 confirm orthodox virus (OPX) cases
  • 1 confirmed monkeypox (case in MA)
Monkeypox: signs and symptoms

• Lesions are circumscribed, deep seated often with umbilication
• Lesions are similar in size and same stage of evolution on a single site of the body (pustules in face or vesicles in legs)
• Fever (malaise, headache, sore throat, cough, generalized Lymphadenopathies) before rash
• Lesions in mouth (enanthem), body including palms and soles (exanthem: macule, papule, vesicles, pustules, scab)
• Lesions are painful until healing phase when they become crusty and itchy
• Rash resolves patient is no longer contagious once ALL scabs have fallen off
Monkeypox: Rash

Maculo-popular vesicular-pustular lesions of varying sizes on the face
Monkeypox: Palm lesions

Public Health Image Library #12761
Monkeypox Hand lesions
Papular-pustular monkeypox lesions
Classical Clinical Features

Papular vesicular-pustular lesions of varying sizes on the body
Extensive papulo-pustular lesions on the body with crust formation

Monkeypox: signs and symptoms

- **Historically:** Characteristic rash is preceded by moderate to severe prodromal symptoms (fevers, malaise, generalized lymphadenopathy) (as above)

- **Current cases** present with atypical features for unknown reasons at this time
  - Prodromal symptoms mild or absent
  - Although rash is still characteristic; often starting in the genital and perianal areas
  - Sometimes rash does not disseminate
  - Cases are being recognized at outpatient clinics because is easily confused with sexually transmitted infections
**Monkeypox: Transmission**

- Direct or indirect contact with body fluids or lesion materials
- Contact with fomites
- Exposure to respiratory secretions
- Examples of high and intermediate risk exposures
  - Shared towels and bedding (infectious body fluids and scabs may be present)
  - Skin-to-skin contact with a patient who has monkeypox
  - Being inside the patient's room or within 6 feet of a patient during any procedures that may create aerosols from oral secretions, skin lesions, or resuspension of dried exudates, without wearing an N95 or equivalent respirator (or higher) and eye protection
- **Good news:** Not easily transmitted
Monkeypox: Differential Diagnosis

- POX viral diseases
- SmallPox (OPX)
- Chicken Pox (varicella-herpes)
# Clinical Characteristics of POX Viral syndromes

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Smallpox</th>
<th>Monkeypox</th>
<th>Varicella</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Time period</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Incubation period</td>
<td>7–17 d</td>
<td>7–17 d</td>
<td>10–21 d</td>
</tr>
<tr>
<td>Prodromal period</td>
<td>1–4 d</td>
<td>1–4 d</td>
<td>0–2 d</td>
</tr>
<tr>
<td>Rash period (from the appearance of lesions to desquamation)</td>
<td>14–28 d</td>
<td>14–28 d</td>
<td>10–21 d</td>
</tr>
<tr>
<td><strong>Symptoms</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prodromal fever</td>
<td>Yes</td>
<td>Yes</td>
<td>Uncommon, mild fever if present</td>
</tr>
<tr>
<td>Fever</td>
<td>Yes, often ≥40°C</td>
<td>Yes, often between 38.5°C and 40.5°C</td>
<td>Yes, up to 38.8°C</td>
</tr>
<tr>
<td>Malaise</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Headache</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Lymphadenopathy</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Lesions on palms or soles</td>
<td>Yes</td>
<td>Yes</td>
<td>Rare</td>
</tr>
<tr>
<td>Lesion distribution</td>
<td>Centrifugal</td>
<td>Centrifugal&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Centripetal</td>
</tr>
<tr>
<td>Lesion appearance</td>
<td>Hard and deep, well-circumscribed, umbilicated</td>
<td>Hard and deep, well-circumscribed,&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Superficial, irregular borders, “dew drop on a rose petal”</td>
</tr>
<tr>
<td>Lesion progression</td>
<td>Lesions are often in one stage of development on the body; slow progression with each stage lasting 1–2 d</td>
<td>Lesions are often in one stage of development on the body; slow progression with each stage lasting 1–2 d&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Lesions are often in multiple stages of development on the body; fast progression</td>
</tr>
</tbody>
</table>

<sup>a</sup> Differences in the appearance of rash have been noted in vaccinated (vaccination <20 years prior to illness) vs unvaccinated individuals. Vaccinated individuals were noted to have fewer lesions, smaller lesions, and better presentation of regional monomorphism and centrifugal distribution of rash.
Smallpox lesions

Contributed by Dr. John Noble, Jr., The Centers for Disease Control and Prevention (CDC)
MONKEYPOX: Advice x clinicians

- CDC issued health advisory on 5/20
  - Be vigilant to possibility of monkeypox if characteristic rash present*
  - Know that illness is presenting atypically
  - Clinicians working in outpatient clinics may be first to suspect monkeypox
  - Many patients have mild symptoms
  - Easy to confuse with sexually transmitted infection OR varicella zoster virus
- Obtain sexual and travel history; determine if any contacts have/had a similar rash
- Obtain specimens
- Notify health department
- Consider initiating contact tracing and monitoring
- Facilitate laboratory testing
Monkeypox: Advice x Clinicians

Patients
• All specimens reported outside of endemic countries, to date, West African clade of monkeypox (associated with milder illness)
• Supportive care typically enough
• Antivirals are available through consultation with CDC

Contacts
• Monitoring of healthcare personnel should be reported to health department; monitoring is for 21 days
• Post-exposure prophylaxis with 2 U.S. licensed vaccines a possibility depending on risk level*
• Pre-exposure prophylaxis for certain healthcare personnel available
Monkeypox: Infection Control

- Infection control: hospital and home
- Duration of isolation
- Decontamination of contaminated surfaces
- Monkeypox virus does not have the potential to be a pandemic; number of cases worldwide still low
- Cases may be occurring in communities other than those where the initial cases have been identified
## Genital Ulcer Disease: Differential diagnosis

In the clinic

<table>
<thead>
<tr>
<th>Infectious</th>
<th>Non-Infectious</th>
</tr>
</thead>
<tbody>
<tr>
<td>* Herpes simplex virus</td>
<td>* Recurrent aphthous stomatitis</td>
</tr>
<tr>
<td>* Syphilis</td>
<td>* Behcet’s Disease</td>
</tr>
<tr>
<td>* Chancroid</td>
<td>* Trauma</td>
</tr>
<tr>
<td>* Lymphogranuloma venereum (LGV)</td>
<td>* Squamous cell carcinoma</td>
</tr>
<tr>
<td>* Granuloma Inguinale</td>
<td>* Drug-induced</td>
</tr>
<tr>
<td></td>
<td>* Other</td>
</tr>
</tbody>
</table>
Monkeypox: differential diagnosis

In the clinic

**Diffuse Rash**
- Syphilis
- Varicella/VZV
- Disseminated herpes
- Molluscum contagiosum
- Other pox viruses
- Disseminated fungal infections
- Disseminated gonococcal infection

**Proctitis**
- Gonorrhea
- Chlamydia
- HSV
Syphilis vs Monkeypox

Secondary Syphilis vs Monkeypox
Skin lesions varicela zoster
Molluscum contagiosum vs Monkeypox

Molluscum contagiosum

Monkeypox
Disseminated cryptococcosis
Confirmed OPX vs Confirmed Monkeypox

2-step process for testing specimens

• 1. **State labs** that are part of the Laboratory Response Network can perform OPX genetic test (confirms OPX DNA from rash lesions). IF positive = **Confirmed orthodox case**

• 2. Confirmatory testing by real time PCR (only at CDC). IF positive = **Confirmed monkeypox case**
## Diagnostic tests for Monkeypox

<table>
<thead>
<tr>
<th>Test</th>
<th>Pros</th>
<th>Cons</th>
</tr>
</thead>
<tbody>
<tr>
<td>Viral culture/isolation: Live virus is</td>
<td>Can yield a pure, live culture of virus for definitive classification of the species. Orthopoxviruses produce distinctive “pocks” on chorioallantoic membranes; and other cell-based viral culture methods can be used. Patient specimens from lesions are the most reliable for this method, as viremia is not present the entire duration of illness.</td>
<td>The assay takes several days to complete. Patient specimens may contain bacteria, hampering culture attempts. Further characterization must be done for viral identification. Must be performed at a major laboratory with skilled technicians.</td>
</tr>
<tr>
<td>grown and characterized from a patient</td>
<td></td>
<td></td>
</tr>
<tr>
<td>specimen.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Electron microscopy: Negative staining</td>
<td>Can be used to identify viral particles in a biopsy specimen, scab material, vesicular fluid, or viral culture. Can differentiate an Orthopoxvirus from Herpesviridae.</td>
<td>Orthopoxviruses are morphologically indistinguishable from each other. Must be performed at a major laboratory with skilled technicians and an electron microscope.</td>
</tr>
<tr>
<td>produces a clear image of a brick-shaped</td>
<td></td>
<td></td>
</tr>
<tr>
<td>particle, allowing for visual classification of a poxvirus, other than Parapoxvirus</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Immunohistochemistry: Tests for the</td>
<td>Can be used to identify antigens in biopsy specimens. This technique can be used to rule out or identify other suspect agents.</td>
<td>Not specific for monkeypox virus. Must be performed at a major laboratory with skilled technicians.</td>
</tr>
<tr>
<td>presence of Orthopoxvirus-specific</td>
<td></td>
<td></td>
</tr>
<tr>
<td>antigens.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PCR, including real-time PCR: Tests for</td>
<td>Can diagnose an active case using lesion material from a patient. The assay uses viral DNA, which is stable if a specimen is kept in dark, cool conditions. Designed to be specific for monkeypox virus.</td>
<td>Highly sensitive assays where concerns about contamination are warranted. These assays require expensive equipment and reagents. Must be performed at a major laboratory with skilled technicians.</td>
</tr>
<tr>
<td>the presence of monkeypox-specific DNA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>signatures.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anti-Orthopoxvirus IgG: Tests for the</td>
<td>Can be used to assess a previous exposure to an Orthopoxvirus, including a pathogen or smallpox vaccination.</td>
<td>Requires the collection of blood (serum) and a cold chain. This assay is not specific for monkeypox virus. Results will be affected by prior smallpox vaccination. The duration of response is variable. Must be performed at a major laboratory with skilled technicians.</td>
</tr>
<tr>
<td>presence of Orthopoxvirus antibodies.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anti-Orthopoxvirus IgM: Tests for the</td>
<td>Can be used to assess a recent exposure to an Orthopoxvirus, including a pathogen or smallpox vaccination. This assay could be used as a diagnostic for suspect Orthopoxvirus patients with prior smallpox vaccination.</td>
<td>Requires the collection of blood (serum) and a cold chain. This assay is not specific for monkeypox virus. Must be performed at a major laboratory with skilled technicians.</td>
</tr>
<tr>
<td>presence of Orthopoxvirus antibodies.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tetracore Orthopox BioThreat Alert: Tests</td>
<td>Can rapidly diagnose an active case using lesion material from a patient; a point-of-care diagnostic test. Can be performed at ambient temperature with little expertise.</td>
<td>This assay is not specific for monkeypox virus. Needs to be tested in endemic settings. Less sensitive than PCR.</td>
</tr>
<tr>
<td>for the presence of Orthopoxvirus</td>
<td></td>
<td></td>
</tr>
<tr>
<td>antigens.</td>
<td></td>
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</tr>
</tbody>
</table>

Abbreviations: IgG, immunoglobulin G; IgM, immunoglobulin M; PCR, polymerase chain reaction.
Monkeypox: Prevention & treatment
In the Stockpile

Vaccines
• JYNNEOS
• ACAM2000

Treatment
• Tecovirimat
• Vaccinia Immune Globulin Intravenous (VIGIV)
JYNNEOS is a live vaccine produced from the strain Modified Vaccinia Ankara-Bavarian Nordic (MVA-BN), an attenuated, non-replicating orthopoxvirus

- Also known as IMVAMUNE, IMVANEX, MVA
- Licensed by FDA in September 2019

Indication

JYNNEOS is indicated for prevention of smallpox and monkeypox disease in adults 18 years of age and older determined to be at high risk for smallpox or monkeypox infection

https://www.fda.gov/vaccines-blood-biologics/jynneos
ACAM2000

• ACAM2000 is a live vaccinia virus vaccine
• Licensed by FDA in August 2007
• Replaced Dryvax -license withdrawn by manufacturer and remaining vaccine destroyed

• Indication
• ACAM2000 is indicated for active immunization against smallpox disease for persons determined to be at high risk for smallpox infection
• CDC-held Emergency Access Investigational New Drug Protocol allows use for Non-Variola Orthopoxvirus infection (e.g., monkeypox) during an outbreak

https://www.cdc.gov/mmwr/preview/mmwrhtml/mm5708a6.htm
https://www.fda.gov/media/75792/download
# ACAM2000 vs JYNNEOS

<table>
<thead>
<tr>
<th></th>
<th>ACAM2000</th>
<th>JYNNEOS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vaccine virus</td>
<td>Replication-competent vaccinia virus</td>
<td>Replication-deficient Modified vaccinia Ankara</td>
</tr>
<tr>
<td>“Take”</td>
<td>“Take” occurs</td>
<td>No “take” after vaccination</td>
</tr>
<tr>
<td>Inadvertent inoculation and</td>
<td>Risk exists</td>
<td>No risk</td>
</tr>
<tr>
<td>autoinoculation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serious adverse event</td>
<td>Risk exists</td>
<td>Fewer expected</td>
</tr>
<tr>
<td>Cardiac adverse events</td>
<td>Myopericarditis in 5.7 per 1,000 primary vaccinees</td>
<td>Risk believed to be lower than that for ACAM2000</td>
</tr>
<tr>
<td>Effectiveness</td>
<td>FDA assessed by comparing immunologic response and “take” rates to Dryvax*</td>
<td>FDA assessed by comparing immunologic response to ACAM2000 &amp; animal studies</td>
</tr>
<tr>
<td>Administration</td>
<td>Percutaneously by multiple puncture technique in single dose</td>
<td>Subcutaneously in 2 doses, 28 days apart</td>
</tr>
</tbody>
</table>
Tecovirimat

- Tecovirimat is an antiviral medication that is approved by the FDA for the treatment of human smallpox disease in adults and pediatric patients weighing at least 3 kg
- Also known as TPOXX or ST-246
- Oral capsule and IV formulations approved by FDA in July 2018 and May 2022, respectively
- Indication
  - Tecovirimat is indicated for the treatment of human smallpox disease in adults and pediatric patients weighing at least 3 kg
  - CDC-held Emergency Access Investigational New Drug Protocol allows use of Tecovirimat for Non-Variola Orthopoxvirus Infection (e.g., monkeypox)
  - Includes allowance for opening an oral capsule and mixing its content with liquid or soft food for pediatric patients weighing less than 13 kg
- Available from the Strategic National Stockpile as an oral capsule formulation or an intravenous vial

https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/208627s000lbl.pdf
Guidance for treatment of monkeypox

• Persons who should be considered for treatment following consultation with CDC might include:
  • Persons with severe disease (e.g., hemorrhagic disease, confluent lesions, sepsis, encephalitis, or other conditions requiring hospitalization)
  • Persons who may be at high risk of severe disease:
    • Persons with immunocompromise
    • Pediatric populations, particularly patients younger than 8 years of age
    • Pregnant or breastfeeding women
    • Persons with one or more complications (e.g., secondary bacterial skin infection; gastroenteritis with severe nausea/vomiting, diarrhea, or dehydration; bronchopneumonia; concurrent disease or other comorbidities)
  • Persons with monkeypox virus aberrant infections that include its accidental implantation in eyes, mouth, or other anatomical areas where monkeypox virus infection might constitute a special hazard (e.g., the genitals or anus)
Vaccinia immune globulin intravenous (VIGIV)

- VIGIV is licensed by FDA for the treatment of complications due to vaccinia vaccination, including:
  - Eczema vaccinatum
  - Progressive vaccinia
  - Severe generalized vaccinia
  - Vaccinia infections in individuals who have skin conditions
  - Aberrant infections induced by vaccinia virus (except in cases of isolated keratitis)
- CDC-held Emergency Access Investigational New Drug Protocol allows use of VIGIV for Non-Variola Orthopoxvirus Infection (e.g., monkeypox)

https://www.fda.gov/vaccines-blood-biologics/approved-blood-products/vaccinia-immune-globulin-intravenous-human
Prophylaxis
Post-exposure Prophylaxis

* Transmission of monkeypox requires prolonged close interaction with a symptomatic individual

* Brief interactions and those conducted using appropriate PPE in accordance with Standard Precautions are not high risk and generally do not warrant PEP
Pre-Exposure Prophylaxis

* On November 3, 2021, the Advisory Committee and Immunization Practices (ACIP) voted to recommend vaccination for select persons at risk for occupational exposure to orthopoxviruses

* Research laboratory personnel, clinical laboratory personnel performing diagnostic testing for orthopoxviruses, and for designated response team members at risk for occupational exposure to orthopoxviruses.

* Healthcare personnel who administer ACAM2000 or care for patients infected with replication competent orthopoxviruses based on shared clinical decision-making.
Medical Countermeasure Requests

- Medical Countermeasures for Monkeypox can be requested from the CDC Emergency Operations Center (770-488-7100)
- Requests for vaccines for PEP, Tecovirimat, or VIGIV should come from State or Territorial Health Authorities
- These products will be supplied by the Strategic National Stockpile
- Vaccine for PrEP will be supplied by CDC Drug Service
- CDC is available for consultations to assist with medical countermeasure utilization including appropriate vaccine and antiviral use
Acknowledgment

• Shyam Kottilil, MD, PhD
• Centers for Disease Control and Prevention
THANK YOU!
QUESTIONS?