MAJOR ARTICLE

# Clinical Characteristics of Human Monkeypox, and Risk Factors for Severe Disease

**Gregory D. Huhn,[1,a] Audrey M. Bauer,[3] Krista Yorita,[2] Mary Beth Graham,[4] James Sejvar,[2] Anna Likos,[2] Inger K. Damon,[2] Mary G. Reynolds,[2] and Matthew J. Kuehnert[2]**

[1]Epidemic Intelligence Service, Division of Applied Public Health Training, Epidemiology Program Office, and [2]Division of Viral and Rickettsial Diseases, National Center for Infectious Diseases, Centers for Disease Control and Prevention, Atlanta, Georgia; [3]School of Public Health, University of Illinois–Chicago, Chicago; and [4]Infectious Diseases Division, Medical College of Wisconsin, Milwaukee

***Background.*** Human monkeypox is an emerging smallpox-like illness that was identified for the first time in the United States during an outbreak in 2003. Knowledge of the clinical manifestations of monkeypox in adults is limited, and clinical laboratory findings have been unknown.

***Methods.*** Demographic information; medical history; smallpox vaccination status; signs, symptoms, and duration of illness, and laboratory results (hematologic and serum chemistry findings) were extracted from medical records of patients with a confirmed case of monkeypox in the United States. Two-way comparisons were conducted between pediatric and adult patients and between patients with and patients without previous smallpox vaccination. Bivariate and multivariate analyses of risk factors for severe disease (fever [temperature, $\geqslant$38.3°C] and the presence of rash [$\geqslant$100 lesions]), activity and duration of hospitalization, and abnormal clinical laboratory findings were performed.

***Results.*** Of 34 patients with a confirmed case of monkeypox, 5 (15%) were defined as severely ill, and 9 (26%) were hospitalized for >48 h; no patients died. Previous smallpox vaccination was not associated with disease severity or hospitalization. Pediatric patients (age, $\leqslant$18 years) were more likely to be hospitalized in an intensive care unit. Nausea and/or vomiting and mouth sores were independently associated with a hospitalization duration of >48 h and with having $\geqslant$3 laboratory tests with abnormal results.

***Conclusion.*** Monkeypox can cause a severe clinical illness, with systemic signs and symptoms and abnormal clinical laboratory findings. In the appropriate epidemiologic context, monkeypox should be included in the differential diagnosis for patients with unusual vesiculopustular exanthems, mucosal lesions, gastrointestinal symptoms, and abnormal hematologic or hepatic laboratory findings. Clinicians evaluating a rash illness consistent with possible orthopoxvirus infection should alert public health officials and consider further evaluation.

Monkeypox is a smallpox-like illness caused by infection with a zoonotic orthopoxvirus. Human infections were first described in central Africa in 1970 [1–3]. The disease is endemic in the Congo basin countries of Africa and, possibly, west Africa as well; the majority of human cases have been detected in the Congo basin countries [4–8]. Comprehensive clinical information has been difficult to ascertain during these outbreaks, because cases were frequently identified retrospectively, access to medical care was often limited in remote villages, and civil unrest had curtailed several epidemiologic investigations [7, 9]. Knowledge of the clinical manifestations and temporal progression of human monkeypox in adults is limited, and most laboratory markers of systemic viral illness are not well defined [9–12].

In 2003, the first reported outbreak of human monkeypox in the Western Hemisphere occurred in the midwestern United States [13–16]. Infection was linked to direct contact with pet prairie dogs (*Cynomys* species) that became ill after being housed with various imported rodents shipped from Ghana [13, 14]. On 4 June 2003, health alerts distributed by the Wisconsin Department of Public Health and the Illinois Department of Public Health requested reporting of suspect

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[a] Present affiliation: ACCESS Community Health Network, Chicago, Illinois.

Reprints or correspondence: Dr. Matthew J. Kuehnert, Div. of Viral and Rickettsial Diseases, Centers for Disease Control and Prevention, 1600 Clifton Rd., Mailstop A30, Atlanta, GA 30329-4018 (mgk8@cdc.gov).

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cases of unusual rash illness, in response to a cluster of 6 patients with rash and fever symptoms following exposure to ill prairie dogs. A total of 37 patients were confirmed to be infected with monkeypox across the midwestern United States [15]. The evaluation of patient illness in health care settings, such as physicians' offices, emergency departments, and hospitals, allowed health officials to collect a wide range of clinical data on monkeypox-associated illness that were unavailable previously [17]. We examined clinical and laboratory characteristics of confirmed cases of human monkeypox infection in adults and children in the United States in 2003 to assess risk factors for severe disease and hospitalization.

## METHODS

Patients suspected of having monkeypox virus infection were identified through clinical reports and active and passive surveillance by state and local public health departments [13–16]. Specimens collected from individuals with rash lesions were examined at the Centers for Disease Control and Prevention (CDC; Atlanta, GA) for evidence of monkeypox virus. Cases were confirmed on the basis of specimen testing by viral culture, PCR for monkeypox virus and orthopoxvirus, electron microscopy, and/or immunohistochemical analysis.

Data pertaining to demographic information, medical history, smallpox vaccination status, signs, symptoms, duration of illness, and laboratory values (i.e., hematologic and serum chemistry findings) were reviewed and extracted from patient medical records by the authors with a standardized data extraction tool. Onset of illness was defined as the date a case patient reported onset of signs or symptoms (including fever, rash, sweats, chills, lymphadenopathy, headache, stiff neck, red eyes, runny nose, sore throat, cough, wheezing, shortness of breath, chest pain, nausea and/or vomiting, abdominal pain, myalgia, back pain, joint pain, confusion, and conjunctivitis). Rash burden was determined using the following parameters established by the World Health Organization: benign, 5–25 lesions; moderate, 26–100 lesions; grave, 101–250 lesions; and plus grave, >250 lesions. Data were entered using Microsoft Access (Microsoft) and were analyzed using SAS, version 8.01 for Windows (SAS Institute). Signs and symptoms were analyzed as categorical variables, and syndromes were established for common complexes of initial signs and symptoms of illness associated with individual case patients. Hypoxemia was defined as an oxygen saturation of ⩽95% in room air.

The first recorded laboratory values, the maximally deviated laboratory values, and the last recorded laboratory values during illness were selected for analysis. Clinical laboratory measurements were analyzed as continuous and dichotomous variables for deviation from normal values derived from published laboratory reference intervals and values for adult patients and pediatric patients (age, ⩽18 years). The median number of days from onset of illness for all patients who had clinical laboratory measurements collected was chosen to define early versus late time points in the duration of illness. Abnormal or atypical laboratory measurements were defined as laboratory values greater than the reference range, except for platelet count, blood urea nitrogen concentration, and albumin, sodium, potassium, and calcium levels, which were designated as abnormal if values were less than the reference range. Abnormal hematocrit values greater than or less than the reference range were analyzed separately according to sex. Transaminase levels were considered to be elevated if either aspartate aminotransferase or alanine aminotransferase values were greater the reference range. Six routine clinical laboratory measurements associated with viral illness (leukocytosis, lymphocytosis, thrombocytopenia, elevated transaminase levels, elevated alkaline phosphatase level, and hypoalbuminemia) were chosen for analysis. A cut point, defined as a majority of laboratory measurements (i.e., ⩾3) that were in the abnormal range, was established to yield the greatest number of patients with values

**Table 1. Demographic information for 34 patients with confirmed monkeypox infection, United States, 2003**

| Characteristic | No. (%) of patients |
|---|---|
| Sex | |
| Male | 18 (52.9) |
| Female | 16 (47.1) |
| Age >18 years | 24 (70.6) |
| State of residence | |
| Wisconsin | 18 (52.9) |
| Illinois | 9 (26.5) |
| Indiana | 7 (20.6) |
| Ethnicity | |
| White | 29 (85.3) |
| Black | 1 (2.9) |
| Unknown | 4 (11.8) |
| Exposure setting | |
| Home | 19 (55.9) |
| Work | 2 (5.9) |
| Pet store | 4 (11.8) |
| Veterinarian's office | 9 (26.5) |
| Previous smallpox vaccination (age range) | |
| Yes (33–47 years) | 7 (20.6) |
| No (6–31 years) | 24 (70.6) |
| Unknown (28–35 years) | 3 (8.8) |
| Underlying medical condition[a] | 8 (23) |

**NOTE.** There were 37 total confirmed monkeypox cases during the 2003 US outbreak (J. Cono, Centers for Disease Control and Prevention, personal communication)

[a] Includes hepatitis C, hepatitis (unspecified type), asthma, hydrocephaly, pregnancy, lupus nephritis, receipt of a bone marrow transplant, and hemophilia.

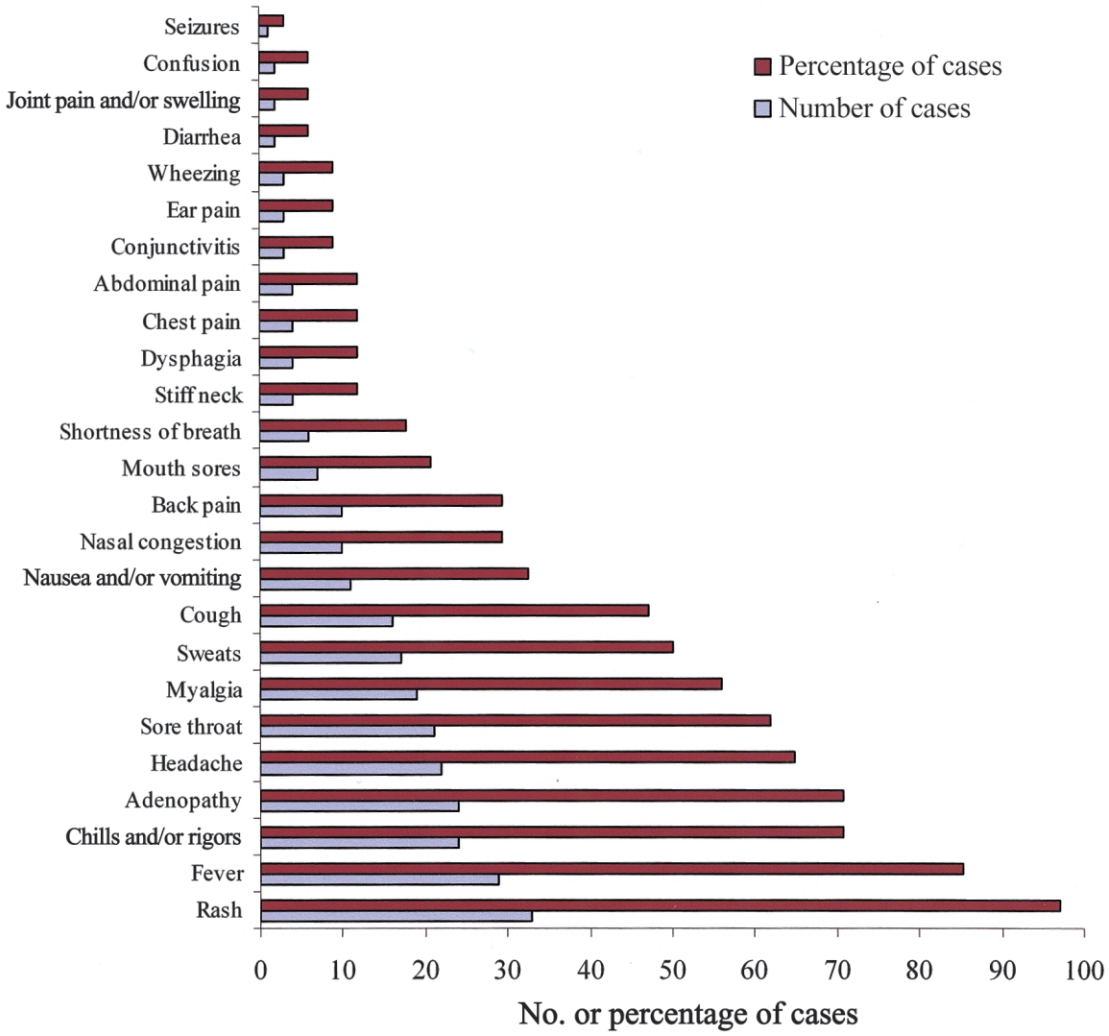


**Figure 1.** Signs and symptoms for 34 patients with confirmed monkeypox, United States, 2003

greater than and/or less than the cut point. Patients with hospitalization durations of >48 h satisfied all inpatient admission criteria. Admission to the intensive care unit was also evaluated.

Severe illness was defined as a temperature of ⩾38.3°C and a rash comprised of ⩾100 lesions at any point during illness. Patients whose rash lesions were not quantified or patients who reported fever without at least 1 recorded temperature measurement were excluded from analysis of illness severity. Bivariate analysis was performed to assess risk factors for each of the following conditions: severe illness, hospitalization >48 h, and ⩾3 abnormal laboratory values. Two-way comparisons were also conducted between pediatric and adult patients and between patients with and patients without reported previous smallpox vaccination. Continuous variables were compared using a 2-sided *t* test. Categorical variables were compared using Fisher's exact test. Laboratory values were compared using Mann-Whitney *U* tests. For multivariate analysis, stepwise logistic regression was used to calculate ORs for all categorical variables that had *P* values <.2 on bivariate analysis. The $\alpha$ of statistical significance was set at <.05.

## RESULTS

Medical records from 34 (92%) of 37 patients with confirmed cases of monkeypox were available for review. Among these 34 cases, 27 (79%) of 34 had quantitative information on fever and rash. A majority of infections (19 cases [56%]) occurred after exposure due to either scratch by, bite by, petting of, or other contact with a monkeypox-infected animal in the home environment. For 29 case patients, the estimated incubation period between the time from initial animal exposure to the onset of illness was 12 days (interquartile range, 11–18 days).

**Table 2. Initial concomitant signs and symptoms at the time of disease presentation to a health care professional for 34 patients with confirmed monkeypox infection, United States, 2003**

| Signs and symptoms | No. (%) of patients |
|---|---|
| Rash and fever | 26 (76) |
| Rash, fever, and adenopathy | 19 (56) |
| Rash, fever, and chills | 18 (53) |
| Rash, fever, adenopathy, and chills | 12 (35) |
| Rash, fever, adenopathy, chills, and headache | 9 (26) |
| Rash, fever, adenopathy, chills, headache, and sore throat | 7 (21) |

The median age of patients was 26 years (range, 6–47 years), and 71% were aged >18 years. A total of 18 patients (53%) were male. Seven patients (21%; median age, 39 years [range, 33–47 years]) reported known previous smallpox vaccination or had recognized smallpox scars. Eight patients (24%) reported an underlying medical condition, including hepatitis C, hepatitis (unspecified type), asthma, hydrocephaly, pregnancy, lupus nephritis, receipt of a bone marrow transplant, and hemophilia (table 1). For all available case patient records, findings of the most recent hematologic and chemistry laboratory analyses before diagnosis of monkeypox infection were normal.

Predominant signs and symptoms of illness included rash (97% of case patients), fever (85%), chills (71%), adenopathy (71%), headache (65%), and myalgias (56%) (figure 1). A majority of patients reported to their health care professional that rash, fever, chills, and adenopathy constituted the initial syndrome at the time of illness presentation (table 2). The median duration of fever was 8 days (range, 2–13 days), and the median duration of rash was 12 days (range, 7–24 days). The median number of days from onset of fever to onset of rash was 2 days (range, 0–12 days). The number of days from onset of fever or rash to other prominent signs and symptoms are listed in table 3. Rash characteristics are listed in table 4 and figure 2. A majority of patients (68%) had lesions that were monomorphic, and 48% of patients had lesions that were distributed centrifugally. Twenty-five percent of patients reported ulcerated or necrotic lesions, and 2 patients noted hemorrhagic pustules.

Laboratory measurements collected for 21 patients with confirmed cases are listed in table 5. There was no statistically significant difference between laboratory findings for blood specimens collected from patients in the early stage of illness versus blood specimens collected from patients during the late stage of illness (median time of sampling, 6 days after illness onset; $P = .09–1.0$). Patients had multiple abnormal laboratory findings, including elevated transaminase levels (50% of patients), low blood urea nitrogen level (61%), hypoalbuminemia (50%), leukocytosis (45%), and thrombocytopenia (35%). The median interval between the onset of illness to observation of

**Table 3. Interval between onset of fever or rash to onset of later prominent signs and symptoms in US patients with monkeypox, by disease severity and age.**

| Interval measured, by initial fever or rash and later sign or symptom | All cases ($n = 34$) | | Severe disease cases ($n = 5$) | | Nonsevere disease cases ($n = 22$) | | Pediatric cases[a] ($n = 10$) | | Adult cases ($n = 24$) | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Interval[b] | No. of patients | Interval[b] | No. of patients | Interval[b] | No. of patients | Interval[b] | No. of patients | Interval[b] | No. of patients |
| Initial fever | | | | | | | | | | |
| To rash | 2 (0–12) | 23 | 0 (0–2) | 5 | 2 (0–5) | 12 | 1 (0–4) | 8 | 2 (0–12) | 15 |
| To nausea and vomiting | 1 (0–9) | 11 | 0 (0–4) | 3 | 1 (0–9) | 6 | 2.5 (0–7) | 4 | 0 (0–9) | 7 |
| To shortness of breath | 5 (0–9) | 5 | 5 | 2 | 0 | 1 | 5 (0–5) | 3 | 6.5 (4–9) | 2 |
| To cough | 0 (0–8) | 13 | 0 (0–2) | 3 | 0 (0–8) | 8 | 0 | 3 | 0 (0–8) | |
| To seizures | 5 | 1 | 5 | 1 | 0 | 0 | 5 | 1 | 0 | 0 |
| To confusion | 2.5 (0–5) | 2 | 5 | 1 | 0 | 1 | 5 | 1 | 0 | 1 |
| To mouth sores | 4 (2–7) | 6 | 4 | 2 | 3.5 (2–7) | 4 | 3.5 (2–4) | 4 | 5.5 (4–7) | 2 |
| Initial rash | | | | | | | | | | |
| To nausea and vomiting | 1 (0–14) | 8 | 0 (0–2) | 3 | 7 (0–14) | 4 | 6 (0–14) | 4 | 0 (0–4) | 4 |
| To shortness of breath | 3 (0–4) | 4 | 3 | 2 | 0 | 1 | 3 (0–3) | 3 | 4 | 1 |
| To cough | 0 (0–9) | 12 | 0 (0–2) | 3 | 0 (0–9) | 7 | 0 (0–9) | 4 | 0 (0–3) | 8 |
| To seizures | 3 | 1 | 3 | 1 | 0 | 0 | 3 | 1 | 0 | 0 |
| To confusion | 3 | 1 | 3 | 1 | 0 | 0 | 3 | 1 | 0 | 0 |
| To mouth sores | 4 (1–11) | 6 | 3 (2–4) | 2 | 7 (1–11) | 4 | 6 (1–11) | 4 | 4 | 2 |

**NOTE.** Cases in which signs or symptoms occurred before fever or rash were excluded.

[a] Age, ≤18 years.

[b] Expressed as median no. of days (range).

**Table 4. Characteristics of rash at the time of examination for US patients with monkeypox.**

| Rash characteristic | Proportion (%) of patients |
|---|---|
| Development | |
| Monomorphic | 21/31 (67.7) |
| Pleomorphic | 9/31 (29.0) |
| No rash | 1/31 (3.2) |
| Distribution | |
| Localized | 8/31 (25.8) |
| Generalized | |
| Centrifugal | 15/31 (48.4) |
| Centripetal | 1/31 (3.23) |
| Even distribution | 7/31 (22.6) |
| Site(s) | |
| Arms and/or hands | 26/32 (81.3) |
| Legs and/or feet | 21/32 (65.6) |
| Head and/or neck | 20/32 (62.5) |
| Chest and/or abdomen | 18/32 (56.2) |
| Back | 15/32 (46.9) |
| Palms | 9/32 (28.1) |
| Groin and/or buttocks | 3/32 (9.4) |
| Soles | 3/32 (9.4) |
| Mucosa (including ocular) | 2/32 (6.3) |
| Severity,[a] maximum no. of lesions | |
| Benign, 5–25 | 14/30 (46.7) |
| Moderate, 26–100 | 10/30 (33.3) |
| Grave, 101–250 | 2/30 (6.7) |
| Plus grave, >250 | 4/30 (13.3) |

**NOTE.** Data are no. of patients with the characteristic/no. evaluated (%). Characteristics were estimated at the height of rash burden. Multiple lesion types may have been present on a patient at the time of examination.

[a] Determined on the basis of World Health Organization criteria.

the most severe abnormal laboratory finding ranged from 3 to 12 days (table 6).

Five patients were defined as being severely ill, and 9 patients were hospitalized as inpatients. Among the severely ill patients hospitalized as inpatients, one was a 6-year old girl who underwent intubation and mechanical ventilation for encephalitis, and one was a 10-year girl with tracheal airway compromise secondary to a large retropharyngeal abscess and cervical lymphadenopathy (figure 3) [20, 21]. Both patients were hospitalized in the intensive care unit. One patient with an underlying comorbidity (hepatitis C) experienced severe disease and was hospitalized as an inpatient. The patient recovered without significant sequelae. Among the adults with complications of infection, one received a diagnosis of bacterial superinfection (unknown microorganism), and one had keratitis and corneal ulceration, which ultimately resulted in a corneal replacement [22]. None of these patients had a preexisting medical condition. No patients died.

Comparison of outcomes for pediatric patients and adult patients revealed that pediatric patients were significantly more likely to be admitted to the intensive care unit, although they were not significantly more likely to develop severe illness. There was no difference in illness severity or inpatient hospitalization in patients with a reported history of smallpox vaccination (table 7). On bivariate analysis, hospitalization for >48 h and presence of dysphagia and hypoxemia were significantly associated with severe disease. Patients with mouth sores who reported dysphagia also had an increased risk of severe disease (table 8). However, on multivariate analysis, there were no significant risk factors associated with severe illness (table 9).

On bivariate analysis, patients with fever (temperature, ⩾38.3°C), rash comprised of >100 lesions, adenopathy, mouth sores, dysphagia (with mouth sores), and nausea and vomiting were more likely to be hospitalized as inpatients. Wisconsin residents and patients exposed to a monkeypox virus–infected pet in the home environment were also more frequently hospitalized as inpatients (table 8). On multivariate analysis, nausea and vomiting were independently associated with a hospitalization duration of >48 h (table 9).

Among patients for whom data on laboratory measurements were available, 6 (30%) had a majority of laboratory values (e.g., ⩾3) that were abnormal. On bivariate and multivariate analysis, patients with mouth sores were significantly associated with having a majority of laboratory values that were abnormal (tables 8 and 9).

## DISCUSSION

The clinical presentation of human monkeypox, described primarily in children and adolescents identified in central and west Africa, has been characterized as a viral prodrome of fever, chills, headache, myalgias, and back pain lasting 1–3 days, followed by a maculopapular exanthema eruption. The rash is predominantly monomorphic in a centrifugal distribution, progresses to vesicular and pustular stages, and crusts during a 2–3-week period [8, 9]. The disease course is often milder than that of smallpox. In contrast to smallpox, pronounced lymph-

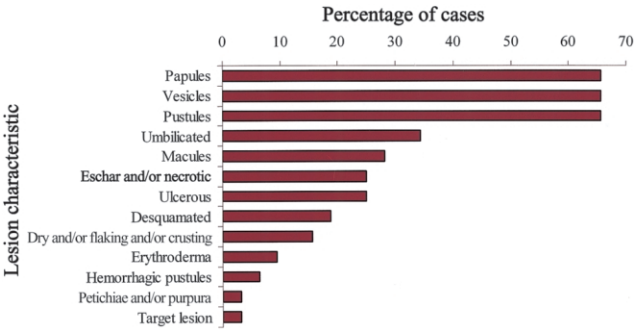


**Figure 2.** Characteristics of monkeypox rash lesions at the time of examination, United States, 2003.

**Table 5. Timing and magnitude of laboratory findings for US patients with monkeypox.**

| Laboratory parameter | Normal adult range | All patients | | Patients with early results of laboratory tests | | Patients with late results of laboratory tests | | $P$[a] |
|---|---|---|---|---|---|---|---|---|
| | | No. evaluated | Median value (range) | No. evaluated | Median value (range) | No. evaluated | Median value (range) | |
| WBC count, cells/mm$^3$ | 4000–9000 | 20 | 7150 (3900–26,800) | 11 | 6200 (3900–17,900) | 8 | 8670 (4780–26,800) | .22 |
| Lymphocytes, % | … | 19 | 26 (14–47) | 11 | 24 (14–44) | 7 | 36 (18–47) | .10 |
| Hematocrit, % | 39–49[b] and 35–45[c] | 20 | 41 (34.3–52) | 11 | 41 (36–50) | 8 | 42 (35.4–52) | .93 |
| Platelet count, $\times 10^9$ platelets/L | 150–400 | 20 | 183 (90–369) | 11 | 154 (126–237) | 8 | 216 (90–369) | .09 |
| Sodium level, mmol/L | 136–145 | 19 | 138 (133–143) | 9 | 137 (135–141) | 9 | 138 (133–141) | 1.0 |
| Potassium level, mmol/L | 3.5–5.0 | 19 | 3.8 (3.2–4.2) | 9 | 3.8 (3.4–4.1) | 9 | 3.9 (3.2–4.2) | .90 |
| Blood urea nitrogen level, mg/dL | 10–20 | 18 | 9.5 (4–15) | 8 | 9.5 (6–12) | 9 | 10 (4–15) | .85 |
| Creatinine level, mg/dL | <1.5 | 18 | 0.8 (0.4–1.1) | 9 | 0.9 (0.1–1.1) | 8 | 0.8 (0.4–0.9) | .31 |
| Calcium level, mmol/L | 9.0–10.5 | 18 | 9.3 (8.3–10.3) | 9 | 9.3 (8.9–9.9) | 8 | 9.4 (8.3–10.3) | .74 |
| Total bilirubin level, mg/dL | 0.3–1.0 | 17 | 0.4 (0.1–1.3) | 8 | 0.4 (0.1–0.6) | 8 | 0.5 (0.2–1.3) | .35 |
| AST level, U/L | 0–35 | 16 | 27.5 (17–95) | 8 | 26 (20–95) | 7 | 38 (17–67) | .82 |
| ALT level, U/L | 0–35 | 17 | 35 (11–186) | 8 | 30 (11–186) | 8 | 45 (15–90) | .39 |
| ALP level, U/L | 40–140 | 17 | 94 (30–209) | 8 | 87 (63–145) | 8 | 103 (30–209) | .39 |
| Albumin level, mg/dL | 3.5–5.5 | 16 | 3.7 (1.1–4.2) | 8 | 3.8 (3.5–4.2) | 7 | 3.7 (1.1–4.0) | .34 |

**NOTE.** Early results of laboratory tests were available <6 days after illness onset, and late results were available ⩾6 days after illness onset. ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase.

[a] Comparison of median values of early vs. late results of laboratory tests.

[b] For men.

[c] For women.

adenopathy is a distinctive hallmark of monkeypox. The clinical signs and symptoms observed during the outbreak in the United States illustrate a similar pattern, although the median duration of rash was slightly shorter, and back pain was not a frequent complaint. The orthopoxvirus involved in the US outbreak was identified as a west African variant [16], whereas most previous clinical descriptions involved persons, mainly children, who were presumably infected with central African variants of the virus. Also, in contrast to African epidemics, the majority of reported cases in the United States were in adults. These features could account for some of the observed differences in clinical description between patients in the United States and patients in Africa.

In smallpox, hematologic abnormalities of lymphocytosis and thrombocytopenia have been observed early in severe confluent forms of infection [23–25]. Information on general clinical chemistry findings in smallpox infection is lacking in the published literature. We describe the first comprehensive assessment of clinical laboratory findings in systemic orthopoxvirus infection. Our data demonstrate that leukocytosis, elevated transaminase levels, low blood urea nitrogen level, and hypoalbuminemia were common features during illness, and lymphocytosis and thrombocytopenia were seen in more than one-third of evaluable patients.

In contrast to monkeypox outbreaks in Africa that affected a disproportionate number of children, none of whom had smallpox vaccine-derived immunity, a majority of cases in the United States occurred in adults, nearly one-third of whom had received the smallpox vaccine before 1972. We observed no significant differences in serious clinical conditions or complications between vaccinated and unvaccinated individuals. However, pediatric patients were hospitalized in intensive care units at significantly higher rates than adults, which may indicate more severe illness or reflect a difference in standard of care. The most critically ill patients in this outbreak were 2 young school-aged children with complications that included encephalopathy and retropharyngeal abscess.

Previous research on smallpox has examined probable physiologic factors influencing morbidity and mortality. Patients with hemorrhagic smallpox, the most lethal form of smallpox, undergo disseminated intravascular coagulation with thrombocytopenia [25, 26]. In this study, only 2 US patients with monkeypox were noted to have had hemorrhagic pustular lesions, and thrombocytopenia was generally mild. No patients were described as having disseminated intravascular coagulation. In patients who have smallpox associated with confluent lesions, copious amounts of fluid accumulate subcutaneously during the vesicular and pustular stages, with weeping of this fluid during the crusting stage. Massive intravascular volume depletion may occur during these stages, frequently leading to shock [27]. In our analysis of monkeypox cases in the United States, hospitalization of patients with mucosal and gastrointestinal clinical symptoms, in addition to low blood urea nitrogen levels and hypoalbuminemia, may have indicated a neg-

**Table 6. Timing and magnitude of abnormal laboratory findings for US patients with monkeypox.**

| Laboratory parameter | Normal adult range | No. (%) of patients with abnormal laboratory findings | Median value (range) of most severe abnormal finding[a] | Median no. of days (range) from illness onset to most severe abnormal finding |
|---|---|---|---|---|
| WBC count, cells/mm$^3$ | 4000–9000 | 9 (45) | 11,000 (9130–26,800) | 7 (4–13) |
| Lymphocytes, % | | 7 (37) | 47 (38–57) | 6 (2–14) |
| Hematocrit, % | 39–49[b] and 35–45[c] | 8 (40)[d] | 33 (30.7–36) and 51 (50–52) | 12 (8–14) and 7 (3–11) |
| Platelet count, $\times 10^9$ platelets/L | 150–400 | 7 (35) | 130 (90–143) | 3 (2–11) |
| Sodium level, mmol/L | 136–145 | 3 (16) | 133 (133–135) | 5 (2–12) |
| Potassium, mmol/L | 3.5–5.0 | 3 (16) | 3.4 (3.2–3.4) | 5 (4–6) |
| Blood urea nitrogen level, mg/dL | 10–20 | 11 (61) | 6 (2–9) | 9 (5–13) |
| Creatinine, mg/dL | <1.5 | 1 | 2.5 | 10 |
| Calcium, mmol/L | 9.0–10.5 | 4 (22) | 8.7 (8.3–8.9) | 6 (5–6) |
| Total bilirubin level, mg/dL | 0.3–1.0 | 1 (6) | 1.3 | 12 |
| AST level, U/L | 0–35 | 8 (50) | 66 (43–95) | 6 (3–14) |
| ALT level, U/L | 0–35 | 10 (59) | 66 (42–186) | 6 (3–14) |
| ALP level, U/L | 40–140 | 1 (6) | 184 | …[e] |
| Albumin level, mg/dL | 3.5–5.5 | 8 (50) | 3.1 (1.1–3.4) | 12 (8–14) |

**NOTE.** Pediatric reference ranges are defined as follows, in accordance with criteria published elsewhere [18, 19]: platelet count: 150–350 $\times 10^9$ platelets/L; lymphocyte percentage: 2%–8% (≤4 years of age), 1.5%–7% (5–6 years of age), 1.5%–6.8% (7–8 years of age), 1.5%–6.5% (9–10 years of age), 1.2%–5.2% (11–16 years of age), and 1.0%–4.8% (17–21 years of age); WBC count: 5–15.5 cells/mm$^3$ (2–6 years of age) and 4.5–13.5 cells/mm$^3$ (7–18 years of age); hematocrit percentage: 34%–37% (2–6 years of age), 35%–40% (7–12 years of age), 36%–43% (boys 13–18 years of age), and 37%–41% (girls 13–18 years of age); alkaline phosphatase (ALP) level: 100–300 U/L (2–10 years of age), 50–375 U/L (boys 11–18 years of age), and 30–300 U/L (girls 11–18 years of age). Reference ranges for albumin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), bilirubin, creatinine, sodium, potassium, and calcium levels are the same as those for adults. No reference range for the blood urea nitrogen level was specified for pediatric patients.

[a] Abnormal laboratory values for the lymphocyte percentage and the AST, ALT, and creatinine levels were all greater than the reference range, whereas abnormal laboratory values for platelet count and the sodium, potassium, blood urea nitrogen, calcium, and albumin levels were all less than the reference range.

[b] For males.

[c] For females.

[d] Two patients had a hematocrit that was less than the reference range, and 6 had a hematocrit that was greater than the reference range.

[e] No date was listed in the medical record for the single adult with an elevated ALP level.

ative protein or improper nutritional balance and the need for volume repletion secondary to gastrointestinal losses. Gastrointestinal fluid losses and hypoalbuminemia are consistent with the movement of fluids from intravascular to extravascular fluid compartments that occurs in systemic infection [28]. These findings, in addition to patients with mouth sores for whom numerous abnormal clinical laboratory findings were observed, suggest that human monkeypox may also cause systemic complications beyond apparent integument and mucosal surface compromise. In experimentally induced infection with aerosolized monkeypox virus in monkeys, lymphatogenous spread of monkeypox virus from viremia affects disseminated lymph nodes and the thymus, spleen, skin, oral mucosa, gastrointestinal tract, and reproductive system [29]. Further study is needed to evaluate the pathophysiology of human monkeypox.

Our study had several limitations. Because this was a retrospective study and patients were not evaluated in accordance with a uniform protocol, we could not measure temporal trends between progression of signs and symptoms of illness and evolution of clinical laboratory values; patients visited health care professionals at different points in their illness, and collection of laboratory specimens and choice of test were at the discretion of the clinician. Also, because there were no deaths in the outbreak, severity of illness was defined by the acuity and burden of fever and rash, rather than by an adverse clinical outcome. This definition may not have been the most accurate index of illness severity. Results of analysis of the severity of illness also may have been affected by the exclusion of 7 patients (21%) who had no recorded temperature or number of rash lesions in the medical records. There were no clinical laboratory test results for 13 patients (38%), none of whom were classified with severe disease or were hospitalized for >48 h. The aggregate laboratory values in our analysis may reflect selection bias towards patients with more-severe manifestations of illness. Lastly, the small sample size led to decreased precision in the risk factor analyses.

In Africa, mortality due to monkeypox infection has ranged from 1.5% to 17% and occurs overwhelmingly in children, a

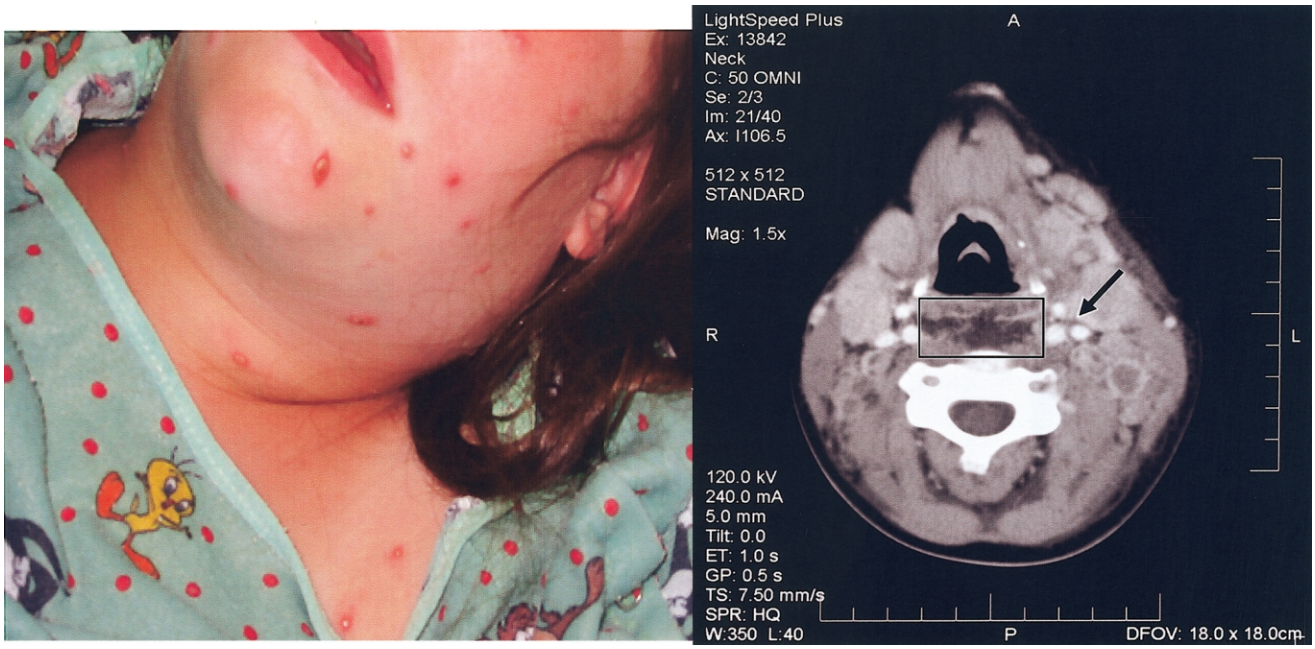


**Figure 3.** Physical (*left)* and radiographic *(right)* characteristics of monkeypox infection for a girl aged 10 years with a retropharyngeal abscess, tracheal impingement, and cervical lymphadenopathy, United States, 2003.

regrettable consequence most likely due to inaccessible medical care [30]. One-fifth of pediatric patients in the US outbreak developed serious complications that could have resulted in death if intensive medical intervention was not available. The identification of risk factors and abnormal laboratory findings described in our analysis may help clinicians determine the need for hospitalization in future possible outbreaks, should monkeypox reemerge in the United States [16].

The most common diagnostic challenge that confronted investigators during monkeypox outbreaks in Africa was distinguishing monkeypox vesicular rash eruptions from those of chickenpox [31]. In the largest reported outbreaks, which occurred in the Democratic Republic of Congo during 1996–1998 and in 2001, interpretation of clinical data specific to monkeypox disease was restricted by potential case misclassification, owing to significant cocirculation of varicella virus in affected communities, and by the small fraction of cases confirmed by diagnostic laboratory analysis [7, 8]. Chickenpox has a shorter and milder prodrome and clinical course, lymphadenopathy is infrequent, lesions usually evolve pleomorphically in a centripetal distribution, and death is extremely rare [31, 32]. The additional descriptions presented here may assist in more

**Table 7. Comparison of basic recorded indicators of monkeypox illness severity for adults and children and for patients with and patients without a history of smallpox vaccination.**

| Indicator of potential illness severity | Proportion (%) of pediatric patients[a] | Proportion (%) of adult patients | $P^b$ | Proportion (%) of patients with prior vaccination | Proportion (%) of patients without prior vaccination | $P^b$ |
|---|---|---|---|---|---|---|
| Fever | | | | | | |
| Temperature of ⩾38.3°C | 7/10 (70) | 11/18 (61) | .70 | 4/5 (80) | 12/21 (57) | .62 |
| Duration of ⩾7 days | 3/7 (43) | 7/11 (64) | .63 | 3/5 (60) | 6/12 (50) | 1.00 |
| Rash comprised of >100 lesions | 3/9 (33) | 3/22 (14) | .32 | 1/6 (17) | 5/22 (23) | 1.00 |
| Cervical lymphadenopathy | 6/10 (60) | 13/24 (54) | 1.00 | 3/7 (43) | 14/24 (58) | .67 |
| Hospitalized for >48 h | 4/9 (44) | 6/22 (27) | .42 | 2/7 (29) | 6/22 (27) | 1.00 |
| Admitted to ICU | 5/10 (50) | 2/23 (9) | .02 | 1/7 (14) | 5/24 (21) | 1.00 |

**NOTE.** Data are no. of patients with the indicator/no. evaluated (%). ICU, intensive care unit.

[a] Age, ⩽18 years.

[b] By the 2-sided Fisher's exact test.

**Table 8. Bivariate analysis of characteristics associated with severe illness outcomes for monkeypox, as defined by intensity of rash and fever, duration of hospitalization, or number of abnormal laboratory findings.**

| | Index of illness severity (no. of patients with severe outcomes) | | | | | |
|---|---|---|---|---|---|---|
| | Intense rash and fever[a] ($n$ = 5) | | Hospitalized for >48 h ($n$ = 9) | | ⩾3 of 6 laboratory tests (⩾50%) with abnormal results ($n$ = 6) | |
| Characteristic | RR (95% CI) | $P$[b] | RR (95% CI) | $P$[b] | RR (95% CI) | $P$[b] |
| Hospitalized for >48 h | **Undefined** | **.01** | NA | NA | 4.4 (0.6–32.8) | .14 |
| Hypoxemia | **Undefined** | **.03** | Undefined | .29 | 1.9 (0.4–9.2) | .50 |
| Dysphagia[c] | **Undefined** | **.03** | 2.7 (0.9–7.4) | .19 | 1.2 (0.2–7.0) | 1.0 |
| Wisconsin resident | 0.5 (0.1–2.7) | .63 | **0.2 (0.1–0.9)** | **.04** | 0.5 (0.1–2.0) | .36 |
| Home exposure | 2.7 (0.4–21.4) | .62 | **6.6 (0.9–46.5)** | **.02** | 3.6 (0.5–26.8) | .18 |
| Fever (temperature of ⩾38.3°C) | NA | NA | **Undefined** | **.02** | Undefined | .52 |
| Rash (>100 lesions) | NA | NA | **3.7 (1.5–9.0)** | **.03** | 2.8 (0.8–9.6) | .26 |
| Adenopathy | 1.7 (0.2–12.8) | 1.00 | **Undefined** | **.03** | 1.2 (0.2–7.5) | 1.00 |
| Nausea and vomiting | 3.0 (0.6–14.7) | .30 | **6.4 (1.6–25.5)** | **<.01** | 1.1 (0.3–4.3) | 1.00 |
| Mouth sores[c] | 5.0 (0.9–20.6) | .09 | **4.3 (1.6–11.8)** | **.01** | **6.4 (1.6–25.1)** | **.01** |

**NOTE.** Statistically significant data are in bold face. Risk ratios (RRs) are indicated as undefined if the value could not be computed because at least 1 patient was not associated with 1 of the 4 possible "character states" (i.e., presence of characteristic with severe outcome, presence of characteristic without severe outcome, absence of characteristic with severe outcome, and absence of characteristic without severe outcome). In each instance in which the RR was undefined but the $P$ value for the 2-sided Fisher's exact test was ⩽.05, either all patients with severe illness had the character state in question or all patients with the given character state had severe outcomes. No other individual signs and symptoms, laboratory parameters, sex, and vaccination status were statistically significant indicators of severe disease outcome. NA, not applicable.

[a] Defined as >100 lesions and a temperature of ⩾38.3°C.

[b] By the 2-sided Fisher's exact test.

[c] The presence of mouth sores with dysphagia was a significant indicator of severe illness and hospitalization, with RRs of 9.5 (95% CI, 1.2–72.3) and 4.9 (95% CI, 1.6–15.4), respectively.

clearly defining the symptom profile of monkeypox and differentiating it from other childhood exanthems, including varicella.

Monkeypox virus, along with variola virus, is on the select list of biological agents determined to have the potential to pose a severe threat to human health [33]. Recent surveillance and health care preparedness initiatives in the United States have promoted increased awareness of atypical febrile rash syndromes possibly caused by agents of bioterrorism [34, 35]. Given our findings, unusual exanthems or mucosal lesions, particularly in association with lymphadenopathy, gastrointestinal symptoms (e.g., nausea and/or vomiting), and hematologic or hepatic laboratory abnormalities, should prompt inclusion of monkeypox in the differential diagnosis within the appropriate epidemiologic context. Clinicians evaluating a rash illness consistent with orthopoxvirus as a possible cause should alert public health officials and consider urgent evaluation in accordance with recommended algorithms [36].

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**Table 9. Multivariate analysis of signs and symptoms independently associated with severe illness outcomes for monkeypox, as defined by intensity of rash and fever, duration of hospitalization, and number of abnormal laboratory findings.**

| Outcome | Sign or symptom | OR (95% CI) | $P$ |
|---|---|---|---|
| Intense rash and fever | None[a] | … | … |
| Hospitalized for >48 h | Nausea and/or vomiting | 15.8 (2.3–106.2) | .005 |
| ⩾3 abnormal laboratory findings | Mouth sores | 28.0 (2.00–394.3) | .01 |

[a] No sign or symptom was statistically association with this outcome.

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