

Clinical and Epidemiological Characteristics of the 2022 Mpox Outbreak in Spain (CEME-22 Study)

G. Ramírez-Olivencia,^{1,2} M. Velasco Arribas,^{2,3} M. M. Vera García,^{4,5} J. Casabona,^{5,6} M. J. Martínez,^{7,2} and F. J. Membrillo De Novales¹ ; on behalf of the CEME-22 Study Group^a

¹Hospital Central de la Defensa “Gómez Ulla.” Infectious Diseases Unit, Madrid, Spain, ²Grupo de Estudio de Patología Importada, Sociedad Española de Enfermedades Infecciosas y Microbiología Clínica (SEIMC), Madrid, Spain, ³Hospital Fundación Alcorcón, Department of Internal Medicine-Infectious Department, Research Department, Alcorcón, Spain, ⁴Centro Sanitario Sandoval, HIV/STI Unit, Madrid, Spain, ⁵Grupo de Estudio de ITS, Sociedad Española de Enfermedades Infecciosas y Microbiología Clínica (SEIMC), Madrid, Spain, ⁶Centre for Epidemiological Studies on HIV/AIDS and STI of Catalonia (CEEISCAT), Health Department, Generalitat de Catalunya, Badalona, Spain, and ⁷Hospital Clinic, Microbiology Department, Barcelona, Spain

Background. We conducted a multicentric national study (SEIMC-CEME-22), to describe the clinical and epidemiological profile of the mpox outbreak in Spain, including the management of the disease.

Methods. This was a retrospective national observational study conducted by Sociedad Española de Enfermedades Infecciosas y Microbiología Clínica (SEIMC) and Foundation SEIMC-GESIDA. We included patients with a confirmed mpox diagnosis before 13 July 2022, and attended at the Spanish health network (the early phase of the outbreak). Epidemiological, clinical, and therapeutic data were collected.

Results. Of a total of 1472 patients from 52 centers included, 99% of them were cisgender men, mostly middle-aged, and 98.6% were residents in Spain. The main suspected route of transmission was sexual exposure, primarily among MSM. Occupational exposure was reported in 6 patients. Immunosuppression was present in 40% of patients, mainly due to human immunodeficiency virus (HIV). Only 6.5% of patients had been vaccinated against orthopoxvirus. Virus sequencing was performed in 147 patients (all B.1 lineage). Rash was the most frequent symptom (95.7%), followed by fever (48.2%), adenopathies (44.4%) myalgias (20.7%), proctitis (17%), and headache (14.7%). Simultaneously diagnosed sexually transmitted infections included syphilis (n = 129), gonococcal infection (n = 91), HIV (n = 67), chlamydia (n = 56), hepatitis B (n = 14), and hepatitis C (n = 11). No therapy was used in 479 patients (33%). Symptomatic therapies and antibiotics were used in 50% of cases. The most used therapy regimens were systemic corticoids (90 patients), tecovirimat (6 patients), and cidofovir (13 patients). Smallpox immunoglobulins were used in 1 patient. Fifty-eight patients were hospitalized, and 1 patient died.

Conclusions. Mpox outbreak in Spain affected primarily middle-aged men who were sexually active and showed a high rate of HIV infection. A range of heterogeneous therapeutic options was performed.

Keywords. emerging infections; HIV; mpox; STI; tecovirimat.

Mpox disease, caused by the mpox virus (MPXV), has been recognized in humans in Central Africa since the 1970s. Historically, this zoonotic infection presented with diverse symptoms and a distinctive rash. After a prodromal phase of 2–4 days, including symptoms such as fever, weakness, lymph

node swelling, occasional headache, back pain, and muscle aches, a centrifugal rash resembling smallpox emerged. This rash affected various body parts, including the oral mucosa, genitalia, palms, and soles. Over 2–4 weeks, it progressed through stages from macules to scabs, which fell off within 7–14 days [1]. Lesion counts varied, with more lesions correlating with increased disease severity [2].

In the 2022 outbreak, there was a significant demographic shift, primarily affecting men, especially men who have sex with men, contrasting with previous outbreaks that mainly affected children. This outbreak also had a high human immunodeficiency virus (HIV) prevalence [3, 4], distinct symptoms like changes in skin lesions, and the emergence of unique symptoms such as rectal pain. Hospitalization rates and healthcare demands were higher than in previous outbreaks [5, 6]. Before 2022, mpox cases were classified based on the number of skin lesions, with pre-2022 cases showing moderate and post-2022 cases mild severity [7]. Rash locations varied, with post-2022 cases showing involvement of the genitalia, trunk, upper limb, and anal/perianal area [8].

Received 15 September 2023; editorial decision 13 February 2024; accepted 22 February 2024; published online 26 February 2024

^aStudy Group team members are listed in the Acknowledgments.

Presented in part: 28th European Congress of Clinical Microbiology and Infectious Diseases (ECCMID 2023), Copenhagen, Denmark, April 15–18, 2023 and 26th Congress of the Spanish Society of Infectious Diseases and Clinical Microbiology (SEIMC 2023), Santiago de Compostela, Spain, June 1–3, 2023.

Correspondence: G. Ramírez-Olivencia, PhD, Hospital Central de la Defensa “Gómez Ulla,” Infectious Diseases Unit, Gta Ejército, 28047 Madrid, Spain (germanro.76@gmail.com).

Open Forum Infectious Diseases®

© The Author(s) 2024. Published by Oxford University Press on behalf of Infectious Diseases Society of America. This is an Open Access article distributed under the terms of the Creative Commons Attribution-NonCommercial-NoDerivs licence (<https://creativecommons.org/licenses/by-nc-nd/4.0/>), which permits non-commercial reproduction and distribution of the work, in any medium, provided the original work is not altered or transformed in any way, and that the work is properly cited. For commercial re-use, please contact reprints@oup.com for reprints and translation rights for reprints. All other permissions can be obtained through our RightsLink service via the Permissions link on the article page on our site—for further information please contact journals.permissions@oup.com.
<https://doi.org/10.1093/ofid/ofae105>

Mpox has 2 genetically distinct clades: clade I (Congo Basin) and clade II (West African). Variations in disease severity exist among different strains of the virus, with clade I exhibiting higher mortality rates (10%) than the milder form caused by clade II (3%) [9]. Despite geographic confinement to specific regions in Africa, isolated cases and sporadic outbreaks had been reported outside these endemic areas [7, 10–12].

On 7 May 2022, the World Health Organization received a notification of a confirmed mpox case involving a traveler from the United Kingdom to Nigeria. Subsequently, mpox cases globally surged, affecting both endemic and nonendemic countries. By October 2022, transmission significantly decreased. Notably, cases with a travel history visited Europe and North America, far from traditional epicenters, highlighting potential alterations in virus biology and shifts in human behavior, affected transmission pathways, reservoirs, and outbreak containment.

The current study aims to comprehensively understand the demographic, epidemiological, and clinical characteristics of mpox during the early phase of the 2022 outbreak in Spain through a multicenter study in diverse healthcare settings. Objectives include describing epidemiological patterns, transmission pathways, associated risk factors, clinical features, laboratory findings and diagnostic approaches for mpox cases during the early outbreak phase.

METHODS

A retrospective, multicenter, observational study was conducted by the Spanish Society for Clinical Microbiology and Infectious Diseases (Sociedad Española de Enfermedades Infecciosas y Microbiología Clínica [SEIMC]) and Foundation SEIMC-GESIDA to investigate mpox virus infection across diverse healthcare facilities in Spain. Nonprobability convenience sampling involved active participation from SEIMC members. The study population included patients from primary care centers, general hospitals, and sexually transmitted infection (STI) clinics. Investigators collected identified cases from each participating center. Demographic, epidemiological, and clinical data were extracted from medical records using a dedicated form.

Inclusion Criteria

Patients testing positive for MPXV genome in a clinical sample by polymerase chain reaction (PCR) or sequencing in Spain before 13 July 2022 were included, regardless of their clinical symptoms. A confirmed mpox case met the 3 types of criteria indicated in the protocol established by the Spanish Ministry of Health to classify the disease (updated as of July 2022): clinical, epidemiological, and laboratory. These criteria were as follows:

1. Clinical: A vesicular rash on any part of the body in a person presenting with ≥ 1 classic symptom or sign of mpox infection (acute illness with fever ($>38.5^{\circ}\text{C}$), intense headache,

myalgia, arthralgia, back pain, or lymphadenopathy), once other diseases have been ruled out.

2. Epidemiological: Any of the following within 21 days before symptom onset in a person with symptoms: close contact with a confirmed or still-under-investigation case of mpox; engagement in high-risk sexual activities; a history of travel to endemic areas of West or Central Africa where virus circulation has been identified.
3. Laboratory: Detection of MPXV genome in a clinical sample by PCR or sequencing.

Exclusion Criteria

Patients meeting inclusion criteria but <18 years old were excluded.

Definitions

Immunocompromised referred to patients with primary immunodeficiency, human immunodeficiency virus (HIV) infection, use of immunosuppressive drugs, or conditions causing temporary or permanent dysfunction of the immune response.

Variables

The study collected demographic and epidemiological data (including transmission mechanism, smallpox vaccination history, and travel history), clinical data (including information on immunodeficiency, cutaneous, gastrointestinal, respiratory, neurological, otorhinolaryngological, genitourinary, and systemic symptoms), and data related to the treatment provided.

Statistical Analysis

Various statistical methods were used, based on data type. Quantitative data were described using mean and standard deviation for normal and median and percentiles for nonnormal distribution. Qualitative data were summarized using total counts and percentages.

Ethical-Legal Aspects

This retrospective observational study with drugs adhered to the definition established in Royal Spanish Decree 957/2020. Personal data were anonymized, and the database was dissociated. Patient inclusion was done through an electronic data collection notebook in an authorized network database (RedCap). The study respected European General Data Protection Regulation, Regulation (EU) 2016/679 (article 13.3). Ethical approval was obtained with an exemption from informed consent due to potential bias in noninclusion. Once approved, conformity was requested from the rest of the participating centers. The researchers committed to guarantee the protection of human rights and human dignity regarding the applications of biology and medicine, following the ethical research standards, including the Helsinki Declaration, the Oviedo Convention, and the Good Clinical Practice guidelines (translation of the Spanish Agency for Medicines and Medical Devices (AEMPS)).

Patient Consent Statement

This work used images obtained from a hospital image bank, where patients had previously provided written consent for educational and research purposes. This approach adhered to ethical standards, as it was approved by the local institutional review board and complied with country-specific regulatory guidelines.

RESULTS

Sociodemographic and Epidemiological Characteristics of Participants at Baseline

A total of 1472 patients were enrolled in the study: 1450 men and 15 women (data missing in 7), including 3 transgender women and 1 transgender man. In Spain, as of 22 July 2022, according to data from the National Network of Epidemiological Surveillance (RENAVE), a cumulative total of 3125 confirmed patients with MPXV had been notified. The mean age of the participants was 38.6 years (standard deviation, 9.3 years). The characteristics of the included population (sex, gender, country of birth, country of residence, and suspected exposure) are presented in [Table 1](#).

The patients' regions of birth are listed in [Table 1](#). It is worth noting that, apart from Spain, the most frequent countries of birth were Italy (39 patients [2.7%]) in the European region, and Venezuela (148 [10.1%]), Colombia (79 [5.4%]), Peru (40 [2.7%]), and Brazil (39 [2.7%]) in the American region.

Table 1. Characteristics of the Included Population in the CEME-22 Study

Characteristic	Patients, No. (%) ^a
Sex	
Male	1450 (99)
Female	15 (1)
Gender	
Cisgender man	1447 (98.8)
Transgender woman	3 (0.2)
Cisgender woman	14 (0.9)
Transgender man	1 (0.1)
Region of birth	
European Region	880 (64.14)
Region of Americas	466 (33.97)
African Region	18 (1.31)
Eastern Mediterranean Region	3 (0.22)
South-East Asia Region	1 (0.07)
Western Pacific Region	4 (0.29)
Region of residence	
European Region	1449 (99.38)
Region of Americas	8 (0.55)
African Region	1 (0.07)
Suspected exposure	
Sexual	1385 (94.1)
Occupational	6 (0.4)
Other	45 (3.1)
Unknown	36 (2.4)

^aPercentages are based on cases with available data.

Of the total, 1437 patients (97.6%) were from Spain, with the Community of Madrid having the highest number of cases at 833 (56.6%). None of the patients had a history of travel to an mpox-endemic area within the preceding 21 days.

The most frequently suspected risk exposure was sexual, in 1385 patients (94.1%), followed by occupational risk in 6 (0.4%) and other types of risk in 45 (3.1%). In 36 patients (2.5%), data regarding the type of exposure could not be retrieved or was unavailable. Although the specific transmission mechanism could not be identified, most of the cases appeared in the context of sexual encounters: male-male in 1295 patients (93.5%), male-female in 19 (1.4%), female-female in 2 (0.1%) and female-male in 4, 0.3%), which could involve ≥ 1 partner. Other types of sexual contact were reported in 17 patients (1.2%). Information on the type of sexual exposure was not available for an additional 135 (9.8%). Among the 473 individuals with available information on the number of sexual partners in the past 21 days (32.1%), the median was 3 (interquartile range [IQR], 1–6). Among the 1273 for whom information was available (86.5%), prostitution was reported by 59 (4.6%).

Information on smallpox vaccination status was available for 1163 patients (79.0%), with 76 (6.5%) reporting a history of vaccination. Regarding immunodeficiency, data were accessible for 95.9% of the 1412 patients, and 39.5% (557 patients) were reported as immunodeficient. The identified types of immunodeficiency included HIV infection in 549 patients (98.6%), drug-induced immunodeficiency in 3 (0.5%), and hematological disease and primary immunodeficiency in 1 each (0.2%). Four patients had unclassified immunodeficiency. In the HIV patient cohort, viral load data was largely unavailable. CD4 lymphocyte counts were available for only 344 patients, with a median count of 724/ μL and an IQR of 541–984/ μL .

Dermatological Clinical Presentation

When information was available, a total of 1382 patients (95.7% of those with information available [IA]) presented with an exanthem, with the rash present before diagnosis in 999 (84.5%). Monomorphic exanthem (uniform skin lesions) was reported in 654 patients (68.1% of those with IA), and pleomorphic exanthem (diverse skin eruptions occurring together or sequentially) in 306 (31.9%). Rash characteristics were not described in 512 cases (34.8%). The distribution of exanthema was localized in 866 patients (68.2% of those with IA), centrifugally generalized in 312 (24.6%), and centripetally generalized in 92 (7.2%). The most frequent rash location was the genital region, encompassing both the perineum and the groin. Rash distribution was not described in 202 patients (13.7%). Further details on the characteristics of the exanthem are presented in [Table 2](#). The presence of bacterial superinfection of the exanthem (microbiologically confirmed or treated owing to high suspicion) was described in 173 patients (13.2% of those with IA), and abscesses were reported in 17 (1.2%).

Extracutaneous Clinical Presentation

General symptoms are shown in Figure 1. Fever was reported in 691 patients (48.2% of those with IA), followed by swollen lymph nodes in 634 (44.4%), myalgias in 295 (20.7%), shivering/chills in 156 (11.0%), joint pain/arthritis in 128 (9.0%),

Table 2. Characteristics of the Exanthem in the CEME-22 Study

Characteristics of Rash	Patients, No. (%) ^a
Type	
Erythematous	120 (8.7)
Vesicular	645 (46.7)
Pustular	444 (32.1)
Papular	442 (32.0)
Macular	132 (9.6)
Petechial	5 (0.4)
Distribution	
Genitals	749 (55.6)
Upper limbs	512 (37.9)
Perineum	424 (31.9)
Head and neck	389 (29.0)
Thorax	339 (25.2)
Lower limbs	288 (21.5)
Abdomen	243 (18.2)
Back	228 (17.0)
Mucous membranes	178 (13.4)
Groin	125 (9.4)
Buttocks	122 (9.2)
Palms	99 (7.4)
Soles	46 (3.5)

^aPercentages are based on cases with available data. Percentages by type or distribution may exceed 100% owing to coexistence of different forms or involvement of multiple anatomic regions.

sweating in 49 (3.5%), and back pain in 19 (1.3%). Furthermore, the majority experienced these symptoms before their diagnosis, with percentages ranging from 68.5% to 91.8%. Arranging symptoms by median time to diagnosis unveiled the following: back pain (3 days), swollen lymph nodes (4 days), and fever, chills, joint pain/arthritis, myalgia, and sweating (5 days). Cervical adenopathies were reported in 147 patients (23.19% of those with IA), inguinal in 490 (77.29%), and adenopathies in other locations in 36 patients (5.68%). The median number of adenopathies in all patients was 1 (IQR, 1–2).

The most common gastrointestinal symptoms were proctitis, in 241 patients (17% of those with IA) and odynophagia, in 240 (16.9%), followed by diarrhea (in 75 [5.3%]), abdominal pain (in 37 [2.6%]), dysphagia (in 34 [2.4%]), and nausea and/or vomiting (in 28 [2.0%]). These symptoms preceded the diagnosis in the majority of patients: proctitis (in 178 [73.9%]), odynophagia (in 191 [79.6%]), diarrhea (in 64 [85.3%]), abdominal pain (in 28 [75.7%]), dysphagia (in 23 [67.6%]), and nausea and/or vomiting (in 22 [78.6%]). Organizing symptoms based on median time to diagnosis revealed the following: odynophagia and proctalgia (5 days to diagnosis), diarrhea and dysphagia (6 days), and abdominal pain and nausea/vomiting (7 days).

Headache was the most frequently reported neurological symptom, occurring in 210 patients (14.7% of those with IA) and preceding diagnosis in 86.7%. The median time to diagnosis was 5 days. Neck stiffness was reported in only 1 case, and no cases of seizures or confusion syndrome were reported.

Otorhinolaryngological symptoms were also reported, with oral ulcers reported in 95 patients (6.7% of those with IA), nasal congestion in 23 (1.6%), and otalgia in 7 (0.5%). These

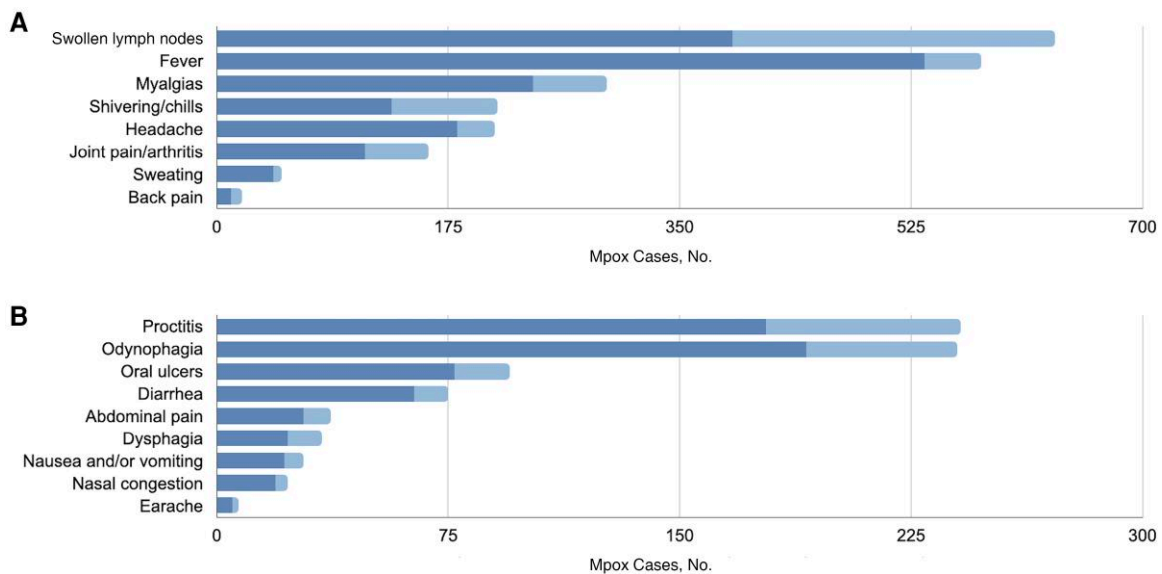


Figure 1. Symptoms of mpox reported in the CEME-22 study. *A*, General symptoms. *B*, Gastrointestinal and ear, nose and throat symptoms. Dark and light bars represent symptoms reported before and after diagnosis, respectively.

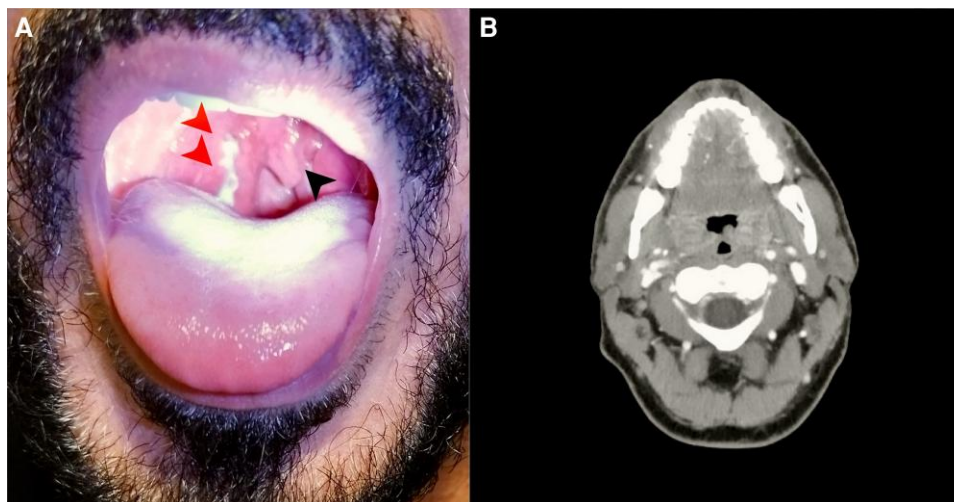


Figure 2. Extracutaneous manifestations in mpox infection. This patient exhibited skin lesions and pharyngeal involvement, experiencing pain and swallowing difficulties. Hospitalization was necessary, with observed improvement after treatment with tecovirimat. *A*, Clinical image displaying pharyngeal involvement with exudate (*red arrowheads*), along with a slight deviation of the uvula (*black arrowhead*). *B*, Computed tomographic scan revealing pharyngeal edema without airway compromise.

symptoms preceded diagnosis in 81%, 81.8%, and 71.4% of patients, respectively, with earache and oral ulcers having a median time to diagnosis of 5 days and nasal congestion a median of 6.5 days. An example of an ear, nose, and throat complication is shown in [Figure 2](#).

Regarding respiratory symptoms, dyspnea was reported in 11 patients (0.8% of those with IA; at the time of diagnosis in 8), cough in 39 (2.7%; before diagnosis in 27), and chest pain in 6 (0.4%; before diagnosis in 3). Chest pain had a median time to diagnosis of 2 days, and dyspnea a median time of 5 days.

Conjunctivitis was described in 11 patients (0.8% of those with IA; before diagnosis in 6), with a median delay of 2 days. Urethritis was reported in 79 (5.6% of those with IA; before diagnosis in 59) (6 days), and paraphimosis in 20 (1.4%; before diagnosis in 8), with a median time to diagnosis of 4 days.

Diagnostic and Laboratory Findings

Diagnosis of the disease was confirmed by PCR analysis of cutaneous lesions in 1387 patients (94.2%), with negative results in 5 (0.4% of those with IA) and 80 in whom the test was not performed on cutaneous specimens (5.4%). PCR analysis was conducted on additional fluid specimens, including urine ($n = 70$; 50.0% positive), blood/serum ($n = 97$; 85.6% positive), pharyngeal exudate ($n = 200$; 76.0% positive), rectal swab ($n = 200$; 79.0% positive) and urethral swab ($n = 50$; 78% positive) samples. Information about the number of cycles (PCR) was available for skin lesion tests ($n = 324$; median, 21 cycles [IQR, 18–25]), urine tests ($n = 20$; 31 cycles [25.5–35.75]), blood tests ($n = 54$; 34 cycles [33–35.25]), pharyngeal exudate tests ($n = 110$; 29 cycles [24–34]), rectal swab sample tests ($n = 94$; 23 cycles [19–33]), and urethral swab sample tests ($n = 22$; 22.5 cycles [19.75–32.25]). Virus sequencing was performed in

147 patients (all B.1 lineage). Serological tests were performed in 1373 (93.3%), with only 54 (3.9%) testing positive.

Laboratory testing at the time of disease diagnosis, including complete blood cell counts and basic biochemistry, was limited. Data for complete blood counts and basic biochemistry were available for only 440 patients (29.9% of the total cohort), with no significant deviations from the reference values of each respective laboratory.

The information regarding coinfection was variable, depending on the diagnostic tests performed at each center. The diagnostic analysis revealed 129 patients with syphilis (41.5% of tested), 91 with gonorrhea (29.3% of tested), 63 with HIV (new infections; 20% of tested), 56 with chlamydia (18% of tested), 13 with hepatitis B virus (4.2% of tested), and 12 with hepatitis C virus (3.9% of tested).

Therapeutic Approach

Fifty-eight patients were hospitalized, and only 1 patient died. Physicians opted for therapeutic abstention in 479 patients (32.5%). Symptomatic and supportive measures were predominantly used, with nonsteroidal anti-inflammatory drugs used in 554 (37.6%), antipyretics in 412 (28.0%), systemic corticosteroids in 90 (6.1%), and hydration (oral or intravenous) in 130 (8.8%).

Topical treatment was administered to 480 patients (32.6%), either alone or in combination. Zinc sulfate was the most frequently used agent ($n = 249$ [51.9%]). Copper sulfate ($n = 230$ [47.9%]), topical antibiotics ($n = 214$ [44.6%]), and corticosteroids ($n = 63$ [13.1%]), were also used.

Antiviral therapy was administered to 47 patients (3.2%). Valacyclovir ($n = 14$ [29.8%]) was the most frequently prescribed drug, followed by cidofovir ($n = 13$ [27.7%]), acyclovir

([n = 8 [17.0%]], tecovirimat (n = 6 [12.8%]), and famciclovir, valganciclovir, and a combination of acyclovir + valacyclovir (each n = 2 [4.3%]). Some patients received systemic antibiotics alone or in combination at the time of first attendance: doxycycline (n = 7), ceftriaxone (n = 5), amoxicillin (n = 2), amoxicillin/clavulanic acid (n = 2), penicillin (n = 2), and clindamycin (n = 1).

DISCUSSION

This study addresses knowledge gaps in clinical, epidemiological, and analytical aspects of mpox during the early phase of the outbreak. Findings have significant implications for disease control, clinical decisions, and public health policies. Insights can enhance diagnostic accuracy, targeted interventions, and patient outcomes in similar scenarios. Encompassing diverse healthcare settings, the study aims to identify presentation, transmission, and treatment variations. This multicenter study may establish an evidence-based foundation for healthcare decisions, policy development, and global mpox mitigation.

Our investigation revealed a prevailing demographic pattern receiving treatment in Spain, notably characterized by a higher prevalence of middle-aged men. While many of these patients are from the local population, there is also a significant presence of foreign individuals from various European countries and the American continent. However, our study's representation of Asian and African populations is limited. Of considerable importance is the absence of identified individuals from predefined endemic regions, underscoring that the majority of those under study are resident within the territorial confines of Spain. This underscores the prominent role of cross-cultural factors in the administration of healthcare. Geographically, a marked concentration of diagnosed individuals is discernible within the community of Madrid, Catalonia, and Andalusia.

Regarding suspected exposure types, sexual contact, particularly among men, was the most common. Mpox requires close contact for transmission, and this type of contact is particularly prevalent in sexual relations. The reported number of sexual partners varied, emphasizing the need for targeted interventions and education on safe practices. Notably, persons associated with prostitution were identified, highlighting the importance of tailored interventions for this specific population [13–16].

Smallpox vaccination shows some effectiveness in preventing mpox [17–19], and its discontinuation may have contributed to mpox spread. The study reveals a low history of smallpox vaccination, indicating potential vaccination coverage gaps, emphasizing the need to promote vaccination among susceptible individuals, especially those with immunodeficiency [20].

This study was planned in the early epidemic phase with a fixed data inclusion deadline, not knowing the epidemic's trajectory. Dealing with numerous variables and addressing

organizational and administrative challenges, especially in a multicenter context within inherent to Spain's regional divisions, posed a substantial obstacle to data updates and the ability to obtain a holistic view of the epidemic. Yet it is within this complexity that we discover the potential for a more comprehensive analysis of the early outbreak phase. The retrospective observational design of the study entails inherent limitations, encompassing potential concerns about the accuracy and comprehensiveness of recorded variables. In addition, the study population was drawn on a voluntary basis from health facilities within the Spanish National Health System. While it encompasses a significant portion of health facilities treating patients with MPXV, the inclusivity of individuals may not uniformly represent the entire affected population during the outbreak. Hence, caution is advised when extrapolating the findings.

Turning to the dermatological aspects, this study underscores the frequent presence of exanthems, highlighting their importance as a diagnostic indicator. We categorized exanthems into monomorphic and pleomorphic types to explore various underlying causes. The distribution and nature of the rash do not offer conclusive diagnostic information or correlate with prognosis [21]; however, some studies (in people with HIV) have shown that ulcerative, necrotic, or confluent lesions are associated with worse prognosis [22]. In fact, local complications are also primarily influenced by the development of bacterial superinfections and abscesses, highlighting the importance of prompt treatment [23, 24]. This study emphasizes the need for comprehensive evaluation of rash distribution and underscores the significance of exanthems in dermatological diagnosis and management. Moreover, this comprehensive study sheds light on the systemic nature of the condition by identifying various extracutaneous manifestations, including general, gastrointestinal, neurological, otorhinolaryngological, and respiratory symptoms. These findings warrant further research to fully understand their frequency, diagnostic implications, and underlying mechanisms [25–30].

In addition, the study confirmed the disease diagnosis through PCR analysis of cutaneous lesions, with positive results also observed in additional fluid specimens. Virus sequencing consistently identified the B.1 lineage. Serological tests yielded a limited number of positive results, aligning with the well-known constraints of serology in diagnosing active disease, making it a less common recommendation. Our study includes these findings owing to their routine collection at the onset of the pandemic. Given the low rate of STI cotesting despite the high prevalence of STI codiagnoses, it would be beneficial to emphasize the importance of full STI screening for individuals suspected of having mpox [3, 31–34].

Our study provides an encompassing perspective on therapeutic interventions during the mpox outbreak. Clinicians implemented diverse treatments, including antivirals, immunoglobulins, steroids, antipyretics, nonsteroidal anti-inflammatory drugs, and local

therapies. Therapeutic abstention was chosen when potential risks outweighed benefits. Symptomatic and supportive measures, along with topical treatments, were predominantly used, while systemic antibiotics were used selectively. The majority of patients with mpox received localized antibiotic therapy for bacterial coinfections or superinfections, with only a minority receiving specific antiviral treatment. Although insufficient scientific evidence universally supports the efficacy of tecovirimat or brincidofovir [5, 35, 36], their *in vitro* activity justifies their recommendation in certain cases. These findings underscore the importance of further research to evaluate the efficacy, safety, and potential side effects of these diverse therapeutic approaches.

Further research endeavors will refine our comprehension of therapeutic efficacy and safety in mpox management, along with enhancing prevention strategies. This entails considering the potential role of asymptomatic infected individuals in community transmission, as well as elucidating specific transmission mechanisms.

Acknowledgments

Members of the CEME-22 Study Group. G. R. O. (Hospital Central de la Defensa “Gómez Ulla,” Madrid, Spain, and Grupo de Estudio de Patología Importada, SEIMC, Madrid, Spain), M. V. A. (Grupo de Estudio de Patología Importada, SEIMC, and Hospital Fundación Alcorcón, Alcorcón, Spain), M. M. V. G. (CS -Centro Sanitario- Sandoval, Madrid, and Grupo de Estudio de ITS -Infecciones de Transmisión Sexual SEIMC), J. C. (Grupo de Estudio de ITS, SEIMC, and CEEISCAT, Badalona, Spain), M. M. M. (Grupo de Estudio de Patología Importada, SEIMC, and Hospital Clinic, Barcelona, Spain), F. J. M. D. N. (Hospital Central de la Defensa “Gómez Ulla”), E. Orviz García (Centro Sanitario Sandoval, Madrid), A. Cabello Ubeda (HU -Hospital Universitario-Fundación Jiménez Díaz, Madrid), P. Muñoz (HU Gregorio Marañón, Madrid), P. Álvarez López (ITS Vall de Hebrón—Drassanes, Barcelona), J. I. Bernardino De La Serna (La Paz, Madrid), I. Pérez Camacho (HRU -Hospital Regional Universitario-Málaga, Málaga, Spain), J. López-Contreras González (H -Hospital- de la Santa Creu y Sant Pau, Barcelona), Á. Gutiérrez Liarte (HU La Princesa, Madrid), P. Ryan (HU, Infanta Leonor, Madrid), G. Jiménez Guerra (H. Can Misses, Ibiza, Spain), M. J. Vivancos Gallego (HU Ramón y Cajal, Madrid), M. J. Urrutikoetxea Gutiérrez (HU Basurto, Bilbao, Spain), M. A. Hernández Betancor (CHU -Complejo Hospitalario Universitario-Insular Materno Infantil de Las Palmas de Gran Canaria, Las Palmas De Gran Canaria, Spain), A. M. Milagro Beamonte (HU Miguel Servet, Zaragoza, Spain), E. Lagaretos González (HU de Gran Canaria Doctor Negrín, Las Palmas De Gran Canaria), A. Muñoz Serrano (HU Puerta de Hierro, Majadahonda, Spain), J. A. Lepe Jiménez (HU Virgen del Rocío, Sevilla, Spain), A. Ruiz Sancho (HUC -Hospital Universitario Clínico-San Cecilio, Granada, Spain), J. Alcoba Flórez (HU Ntra Sra De la Candelaria, Santa Cruz De Tenerife, Spain), Á. Mena De Cea (CHU La Coruña, La Coruña, Spain), M. N. Navarrete Lorite (HU Virgen Macarena, Sevilla), A. Corma-Gómez (HU Virgen de Valme, Sevilla), M.D. Ocete (Consorcio HGU Valencia, Valencia, Spain), M. Simón Sacristán (Hospital Central de la Defensa Gómez Ulla), O. Martín Segarra (Fundación Alcorcón), A. Rivero Román (HU Reina Sofía, Córdoba, Spain), E. Delgado Sánchez (HU San Juan, Alicante, Spain), D. Torrús Tendero (HGU Alicante Dr Balmis, Alicante), B. Valle Borrego (HU Severo Ochoa, Leganés, Spain), S. L. Sanbonmatsu Gámez (HU Virgen de las Nieves, Granada), E. Van Den Eynde (HU, Parc Taulí, Sabadell, Spain), A. Pérez González (H. Álvaro Cunqueiro, Vigo, Spain), F. Artigues Serra (HU Son Espases, Palma De Mallorca, Spain), P. González-Ruano Pérez (HU Infanta Sofía, San Sebastián De Los Reyes, Spain), D. V. Gerez Neira (HU Jerez, Jerez De La Frontera, Spain),

C. Amador-Prous (H. Marina Baixa, Alicante), H. Azkune Galparsoro (HU Donostia, Donostia, Spain), L. Mao Martín (HU Henares, Coslada, Spain), D. García Rosado (HU Canarias, La Laguna, Spain), Ó. Martínez Expósito (HU Cabueñes, Gijón, Spain), G. Soria Fernández-Llamazares (HU Fuenlabrada, Fuenlabrada, Spain), M. Blanco Soto (HC La Línea de la Concepción, La Línea De La Concepción, Spain), M. Á. Morán Rodríguez (HU Araba, Vitoria-Gasteiz, Spain), M. M. Treviño Castellano (CHU Santiago, Santiago De Compostela, Spain), M. M. Masiá (HGU Elche, Elche, Spain), A. M. Castillo Navarro (HGU Virgen de la Arrixaca, Murcia, Spain), M. A. Sepúlveda Berrocal (HGU Toledo, Toledo, Spain), L. Sánchez Gómez (HU Burgos, Burgos, Spain), A. Vallejo Alonso (HU Fuerteventura, Fuerteventura, Spain), E. Álvarez Artero (CAU Palencia H. Río Carrión, Palencia, Spain), M. D. C. Sáez Barber (H. Sagunto, Sagunto, Spain), E. Bernal Morell (HU Reina Sofía, Murcia), Ó. Ayerdi (CSSandoval, Madrid), I. Carrillo Acosta (HU Fundación Jiménez), C. Veintimilla (HU Gregorio Marañón), P. Vidovic-Mendoza (ITS Vall de Hebrón—Drassanes), M. Mora (La Paz), and B. Baza (CS Sandoval, Madrid).

Financial support. This work was supported by Foundation SEIMC-GESIDA, Spain.

Potential conflicts of interest. All authors: No reported conflicts.

References

- Petersen E, Kantele A, Koopmans M, et al. Human monkeypox: epidemiologic and clinical characteristics, diagnosis, and prevention. *Infect Dis Clin North Am* **2019**; 33:1027–43.
- Jezeek Z, Szczeniowski M, Paluku KM, Mutombo M. Human monkeypox: clinical features of 282 patients. *J Infect Dis* **1987**; 156:293–8.
- Ortiz-Saavedra B, Montes-Madariaga ES, Cabanillas-Ramirez C, et al. Epidemiologic situation of HIV and monkeypox coinfection: a systematic review. *Vaccines (Basel)* **2023**; 11:246.
- Gandhi AP, Padhi BK, Sandeep M, et al. Monkeypox patients living with HIV: a systematic review and meta-analysis of geographic and temporal variations. *Epidemiologia (Basel)* **2023**; 4:352–69.
- Li P, Li J, Ayada I, et al. Clinical features, antiviral treatment, and patient outcomes: a systematic review and comparative analysis of the previous and the 2022 mpox outbreaks. *J Infect Dis* **2023**; 228:391–401.
- Sharif N, Sharif N, Alzahrani KJ, et al. Molecular epidemiology, transmission and clinical features of 2022-mpox outbreak: a systematic review. *Health Sci Rep* **2023**; 6:e1603.
- Huhn GD, Bauer AM, Yorita K, et al. Clinical characteristics of human monkeypox, and risk factors for severe disease. *Clin Infect Dis* **2005**; 41:1742–51.
- Hatami H, Jamshidi P, Arbabi M, et al. Demographic, epidemiologic, and clinical characteristics of human monkeypox disease pre- and post-2022 outbreaks: a systematic review and meta-analysis. *Biomedicine* **2023**; 11:957.
- Bunge EM, Hoet B, Chen L, et al. The changing epidemiology of human monkeypox—a potential threat? A systematic review. *PLoS Negl Trop Dis* **2022**; 16:e010141.
- Yong SEF, Ng OT, Ho ZJM, et al. Imported monkeypox, Singapore. *Emerg Infect Dis* **2020**; 26:1826–30.
- Vaughan A, Aarons E, Astbury J, et al. Two cases of monkeypox imported to the United Kingdom, September 2018. *Euro Surveill* **2018**; 23:1800509.
- Erez N, Achdout H, Milrot E, et al. Diagnosis of imported monkeypox, Israel, 2018. *Emerg Infect Dis* **2019**; 25:980–3.
- Chen Y, Li Y, Fu L, et al. Knowledge of human mpox (monkeypox) and attitude towards mpox vaccination among male sex workers in China: a cross-sectional study. *Vaccines (Basel)* **2023**; 11:285.
- Strathdee SA, Crago AL, Shannon K. Harm reduction and rights-based approaches to reduce monkeypox transmission among sex workers. *Lancet Infect Dis* **2023**; 23:e43–6.
- Singer RB, Johnson AK, Zemplak JL, et al. Monkeypox prevention and protecting sex workers: a call to action. *Arch Sex Behav* **2022**; 51:3659–62.
- Jackson KJ, Buchholz M. Ecological study: MSM sex worker advertising amidst monkeypox in three U.S. cities. *Public Health Nurs* **2023**; 40:696–701.
- Montero Morales L, Barbas del Buey JF, Alonso García M, et al. Post-exposure vaccine effectiveness and contact management in the mpox outbreak, Madrid, Spain, May to August 2022. *Euro Surveill*. **2023**; 28:2200883.
- Dalton AF, Diallo AO, Chard AN, et al. Estimated effectiveness of JYNNEOS vaccine in preventing mpox: a multijurisdictional case-control study—United States, August 19, 2022–March 31, 2023. *MMWR Morb Mortal Wkly Rep* **2023**; 72:553–8.
- Deputy NP, Deckert J, Chard AN, et al. Vaccine effectiveness of JYNNEOS against mpox disease in the United States. *N Engl J Med* **2023**; 388:2434–43.

20. Titanji BK, Eick-Cost A, Partan ES, et al. Effectiveness of smallpox vaccination to prevent mpox in military personnel. *N Engl J Med* **2023**; 389:1147–8.
21. Yon H, Shin H, Shin JI, et al. Clinical manifestations of human mpox infection: a systematic review and meta-analysis. *Rev Med Virol* **2023**; 33:e2446.
22. Mitjà O, Alemany A, Marks M, et al. Mpox in people with advanced HIV infection: a global case series. *Lancet* **2023**; 401:939–49.
23. Gamo Guerrero M, Simón Gozalbo A, Martín Díaz M, et al. Interdisciplinary management of mpox-related local complications: report on a series of cases. *Front Med (Lausanne)* **2023**; 10:1184924.
24. Estévez S, Vara M, Gamo M, et al. Epidemiological and clinical characteristics of patients admitted to a secondary hospital with suspected MPOX virus infection: is HIV playing a role? *J Clin Med* **2023**; 12:4124.
25. Simadibrata DM, Lesmana E, Pratama MIA, Annisa NG, Thenedi K, Simadibrata M. Gastrointestinal symptoms of monkeypox infection: a systematic review and meta-analysis. *J Med Virol* **2023**; 95:e28709.
26. Badenoch JB, Conti I, Rengasamy ER, et al. Neurological and psychiatric presentations associated with human monkeypox virus infection: a systematic review and meta-analysis. *EClinicalMedicine* **2022**; 52:101644.
27. Abdelaal A, Reda A, Hassan AR, et al. Monkeypox-associated manifestations and complications involving the eye: a systematic review and meta-analysis of previous and current outbreaks. *Asia Pac J Ophthalmol (Phila)* **2023**; 12:326–37.
28. Gandhi AP, Gupta PC, Padhi BK, et al. Ophthalmic manifestations of the monkeypox virus: a systematic review and meta-analysis. *Pathogens* **2023**; 12:452.
29. Sayad R, Siddiq A, Hashim A, Elsaediy AS. Can the current monkeypox affect the heart? A systematic review of case series and case report. *BMC Cardiovasc Disord* **2023**; 23:328.
30. Jaiswal V, Sultana Q, Lahori S, et al. Monkeypox-induced myocarditis: a systematic review. *Curr Probl Cardiol* **2023**; 48:101611.
31. Maldonado-Barrueco A, Sanz-González C, Gutiérrez-Arroyo A, et al. Sexually transmitted infections and clinical features in monkeypox (mpox) patients in Madrid, Spain. *Travel Med Infect Dis* **2023**; 52:102544.
32. Girometti N, Byrne R, Bracchi M, et al. Demographic and clinical characteristics of confirmed human monkeypox virus cases in individuals attending a sexual health centre in London, UK: an observational analysis. *Lancet Infect Dis* **2022**; 22:1321–8.
33. Rizzo A, Pozza G, Salari F, et al. Concomitant diagnosis of sexually transmitted infections and human monkeypox in patients attending a sexual health clinic in Milan, Italy. *J Med Virol* **2023**; 95:e28328.
34. Curran KG, Eberly K, Russell OO, et al. HIV and sexually transmitted infections among persons with monkeypox—eight U.S. jurisdictions, May 17–July 22, 2022. *MMWR Morb Mortal Wkly Rep* **2022**; 71:1141–7.
35. Chenchula S, Ghanta MK, Amereni KC, et al. A systematic review to identify novel clinical characteristics of monkeypox virus infection and therapeutic and preventive strategies to combat the virus. *Arch Virol* **2023**; 168:195.
36. Fox T, Gould S, Princy N, Rowland T, Lutje V, Kuehn R. Therapeutics for treating mpox in humans. *Cochrane Database Syst Rev* **2023**; 3:CD015769.