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from urine, blood, or genital lesions.[2] However, the exact mechanism of this event remains controversial in the literature. Although Lapa and colleagues[1] reported that cross-contamination from other sources (blood and urine) is unlikely due to the absence of viral DNA in their specimens, this finding should be interpreted with caution due to some points. First, the finding is based on the results obtained from a single patient. Therefore, an appropriate conclusion is not attainable from this report. Moreover, Noe and colleagues[3] showed no growth when culturing the monkeypox virus seminal samples of two patients with monkeypox using VeroE6 cell lines.

Second, previous investigations have detected monkeypox viral DNA in the blood and urine samples of patients with monkeypox. For example, Thornhill and colleagues[4] reported monkeypox viral DNA-positive PCR results in 7% of blood samples and 3% of urine samples taken from a total of 528 patients with monkeypox. Although these rates are meager, they should be considered, especially because positive blood and urine samples were further reported in other relevant investigations.[3,5] Detecting viral shreds in these samples might suggest potential semen cross-contamination by these particles. Although the authors excluded this possibility in their patient, the sample size is still a major limitation. Third, cross-contamination of viral particles might also occur from genital lesions (eg, exfoliated epithelial cells). However, the authors did not exclude this possibility because their lesion samples were obtained from the head only. According to the evidence from the authors and other studies,[3] skin lesions have the most extended viral shedding intervals and highest viral concentrations. For example, Thornhill and colleagues[4] reported that samples obtained from skin and anogenital regions had the highest positive PCR results (97%) when compared with other samples. Moreover, Tarín-Vicente and colleagues[6] reported that 99% of skin swabs and 78% of anal swabs were positive in their monkeypox population. These findings indicate the potential ability of these lesions to induce cross-contamination with seminal fluids. However, this was not also specified by Lapa and colleagues.

Furthermore, monkeypox viral detection in semen is not sufficient to indicate its sexual transmission since evidence from previous studies on other viruses that caused viremia and could be detected in semen did not indicate their sexual transmission[2,7] Detecting viral particles within the male reproductive system is commonly secondary to viraemia because the blood–testis barrier is liable to viruses, mainly when local or systemic inflammation occurs.[8] Viral persistence through the tract is also likely, irrespective of its ability to replicate because the testes can be an immunologically favored site for the virus. Accordingly, we suggest that the current evidence be carefully interpreted until other investigations confirm the findings.

We declare no competing interests.

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Authors' reply

We thank Abdullah Reda and colleagues for their comments on our work.[1] We agree that the possibility that sources for the detection of monkeypox virus genomes in the semen could derive from passive diffusion from other body fluids or specimen contamination from genital lesions deserves careful consideration, based also on previous experience with other human viruses. However, several findings make this possibility unlikely in our case. A possible mechanism favouring diffusion from the blood to the genital tract is increased blood barrier permeability due to inflammatory conditions such as orchitis. Existing evidence shows that orchitis during smallpox was exceedingly rare, and inflammation in the genital tract was excluded in the patient. Moreover, as pointed out in our Comment,[1] we found that monkeypox virus PCR test for urine was negative. Furthermore, this PCR test had a much higher cycle threshold than semen in peripheral blood samples collected within the same timeframe, thus making it unlikely that semen was contaminated by these fluids. Finally, to avoid monkeypox virus contamination from the only genital lesion located on the penis, we required the hands and penis to be

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cleaned before sample collection and clear instructions were given for excluding contact or lesion abrasion during the collection of the semen sample.

That contamination by exogenous sources represents the only or the major cause for the presence of monkeypox virus in semen samples is also deemed unlikely in several studies addressing the monkeypox virus distribution in different body sites. In a large case series of monkeypox,[2–4] 58 (75%) of 77 patients had monkeypox virus DNA in their semen, supporting that it is a too frequent finding for relegating it to mere contamination. Studies of other viruses also highlight the difficult or sporadic isolation of replication-competent viruses from semen. Infectious Zika virus was isolated from 3 (4%) of 78 semen samples with detectable viral RNA, thus suggesting that the absence of viral isolation could be at least in part attributed to technical limitations rather than the absence of virus in the seminal fluid.[5]

Notably, we have achieved monkeypox virus isolation by culturing semen from a second patient with monkeypox who was followed up at the National Institute for Infectious Diseases 'Lazzaro Spallanzani', with a quantification cycle value of 22·7. We agree that epidemiological and laboratory data from large cohorts are needed to clarify the potential role played by semen in monkeypox virus transmission, and that a more in-depth analysis of seminal tropism of monkeypox virus should be performed to assess whether viral particles or DNA are associated to the cellular fractions (ie, seminal leukocytes, exfoliated epithelial cells, or sperm cells) or to seminal plasma. However, it is worthy to mention that, when it comes to veterinary poxviruses, evidence already exist for semen-driven transmission.[6]

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Full-dose NSAIDs at the first sign of respiratory infection?

In their Review article in *The Lancet Infectious Diseases*, Norberto Perico and colleagues[1] recommend administration of non-steroidal anti-inflammatory drugs (NSAIDs) at the first sign of respiratory infection, without waiting for a confirmation of COVID-19. This recommendation contradicts both the ritual assertion that inflammation initially plays a defensive role against infections, and the results of two large randomised controlled trials showing an unfavourable and unsafe role of ibuprofen in managing respiratory infections.[2]

The authors acknowledge the more convincing data available for indometacin, the only NSAID to be successfully tested in a randomised controlled trial (against paracetamol),[3] with in-vitro antiviral effects against several viruses and SARS-CoV-2,[1] and outperforming a matched group of celecoxib users in a real-world dataset.[4] Nevertheless, their recommended NSAIDs for early COVID-19 symptoms in adults include nimesulide, celecoxib (which has not been successfully tested in randomised controlled trials), ibuprofen (with unfavourable results in randomised controlled trials for respiratory infections),[2] and aspirin (for which an ineffective randomised controlled trial is cited,[1] which was associated with safety problems, as well as other uncited null randomised controlled trials), rather than indometacin.

Finally, the authors support their recommendations by citing two observational studies. Unfortunately, the first retrospective study[5] did not meet its primary outcome; time to resolution of major symptoms was not significantly shorter with their algorithm, but significantly longer (18 days *vs* 14 days, p=0·033), suggesting that the recommendation of full-dose NSAIDs at onset of viral multiplication is not suitable for all patients, although it can be useful for a subgroup of patients with a high inflammatory state. Incidentally, the Bonferroni adjustment for the 18 comparisons shown in the study by Gordon and colleagues[5] leads to a p value cutoff of 0·0050, which means the difference reported in the secondary outcome of hospitalisation is not statistically significant either.[5]

Therefore, the authors correctly conclude that randomised controlled trials are required to consolidate their positive observational findings.[1]

I declare no competing interests.

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See **Online** for appendix