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Middle East respiratory syndrome: new disease, old lessons

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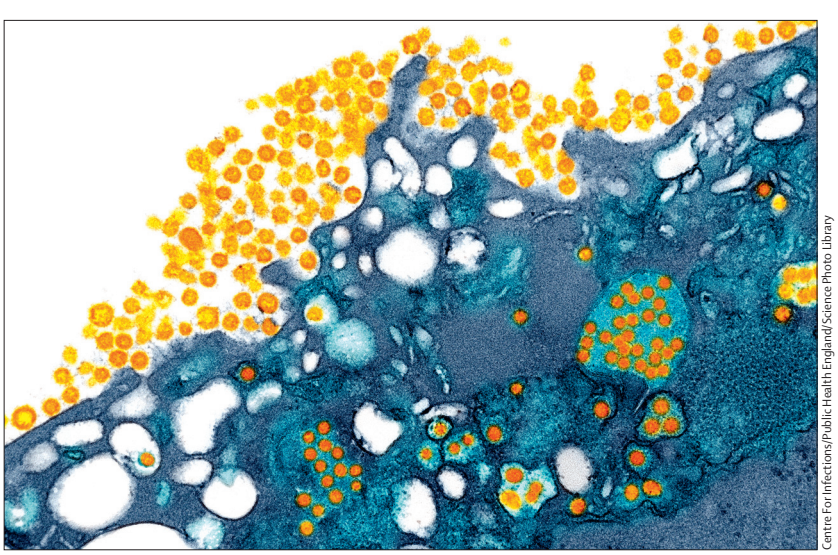
In 2003, severe acute respiratory syndrome coronavirus caused an epidemic of severe viral pneumonia. The emergence of Middle East respiratory syndrome coronavirus (MERS-CoV) has raised concerns of a similar epidemic. Although 55 laboratory-confirmed cases have been reported to WHO,[1] published clinical details are sparse. In *The Lancet*, Benoit Guery and colleagues[2] give a detailed description of two cases, occurring without co-infection. This report is important not only because it provides information about the clinical features of the disease, but also because it confirms human-to-human transmission, shows the importance of travel and contact history-taking, draws attention to the need for analysis of lower respiratory tract specimens to exclude disease, and suggests that previous estimates of the incubation period might be too short.

Patient 1, who had previously travelled to the Middle East, presented with fever, chills, and diarrhoea. He had a history of sigmoiditis, hypertension, and renal transplantation, for which he was receiving immunosuppressant drugs. During the 6 days after admission to hospital, he developed respiratory failure needing mechanical ventilation and subsequently extracorporeal membrane oxygenation (ECMO), despite administration of nitric oxide and use of prone ventilation. Patient 2, who had previously shared a hospital room with patient 1, deteriorated more rapidly, needing ECMO within 7 days of re-presentation with respiratory symptoms. Both patients developed acute renal failure, needing renal replacement therapy. Radiological imaging showed progressive bilateral groundglass opacities and consolidation.

The clinical features are much the same as in other reports of severe respiratory failure associated with MERS-CoV infection, with rapid deterioration in respiratory function over days to weeks, associated with acute renal failure.[3-6] Of the patients for whom clinical features have been reported, two had co-infection with influenza[4] or possible bacterial co-infection,[5] which might have contributed to severity, whereas the remaining three patients[3,6]—as with those reported by Guery and colleagues[2]—had severe disease without evidence of co-infection. Diarrhoea has been described in three other patients and seems to be a feature of the disease.[6] Overall, mortality seems to be high; up to now, 31 of 55 patients with laboratory-confirmed disease reported to WHO have died.[1] However, some patients with MERS-CoV infection might present with only mild symptoms.[4,6,7] Because patients with mild symptoms are less likely to be extensively investigated, patients with MERS-CoV infection and mild disease might be under-represented in published case reports and reports to WHO.

The report by Guery and colleagues[2] shows the importance of history-taking in raising suspicion of MERS-CoV infection. Recent travel to the Middle East, combined with evidence of respiratory infection, triggered suspicion and specific testing of respiratory samples for MERS-CoV infection in patient 1. Present WHO guidance is to test for MERS-CoV in patients with severe acute respiratory infection who have recently returned from the Middle East.[1] How recent is recent? Although 10 days has been used as the incubation period,[4] Guery and colleagues note that the incubation period could be as long as 12 days. In view of the evidence of human-to-human transmission,[2,4,7] albeit sporadic, it would also be sensible to ask about respiratory symptoms in those close contacts of patients who have a relevant travel history.

Exclusion of the diagnosis of MERS-CoV infection needs repeated testing of lower respiratory tract specimens. In Guery and colleagues' patients, virus could be reliably detected in specimens obtained by induced sputum or bronchoalveolar lavage, but not in upper respiratory tract specimens.[2] Similar findings have been reported,[3] but in the earlier report the virus was



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MERS coronavirus particles budding from host cell

not consistently detected in lower respiratory tract specimens, being identified in sputum and tracheal aspirate but not bronchoalveolar lavage fluid.

What precautions should be taken to prevent transmission? The extent of human-to-human transmission is unclear but the consequences of infection seem to be severe. Guery and colleagues report that none of 100 health-care staff who were in contact with patient 1 in the early stage of his admission to hospital were infected, despite an absence of personal protective equipment. Similarly, none of 40 community contacts of patient 2 were infected.[2] However, asymptomatic transmission cannot be excluded on the basis of the investigations done, and serological results from contacts of UK cases are still awaited.[4] A serological study of 85 of 123 retrospectively identified contacts of a patient transferred from Qatar to Germany showed no evidence of symptomatic or asymptomatic transmission, but the respiratory specimen taken at the time of transfer had PCR assay and culture results indicative of a low viral load, suggesting that his infectivity was very low.[8] In the absence of conclusive data it would be prudent to isolate individuals suspected of having MERS-CoV infection and to follow guidelines for prevention of airborne transmission.[9] These guidelines should be followed rigorously: in the UK, a visitor with no history of overseas travel and no other recent contact with the index patient developed MERS-CoV after visiting the invasively ventilated index patient for only 2·5 h. During that time she did not wear full personal protective equipment.[4] The patients described by Guery and colleagues shared a bathroom during the period of cross-infection, and further investigations to establish the presence or absence of MERS-CoV in stool specimens could help to elucidate another potential route of spread.

Guery and colleagues' report shows that the key lessons from MERS-CoV are old lessons: take a thorough history, and take adequate steps to protect yourself, your staff, and your patients and their visitors from infection.

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Oseltamivir resistance during treatment of H7N9 infection

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Detection of an Arg292Lys mutation (N2 numbering) in the virus neuraminidase (NA) gene within 2 days of initiating oseltamivir treatment, in the first reported human infection by avian A(H7N9) influenza virus,[1] raised concern about emergence of resistance during treatment with neuraminidase inhibitors. This is important because a Ser31Asn resistance mutation in the M2 protein of A(H7N9) viruses, also present in A(H1N1)pdm09 and seasonal A(H3N2) viruses, abrogates effectiveness of available M2 inhibitors (amantadine and rimantadine). In *The Lancet*, Yunwen Hu and colleagues[2] report the emergence of oseltamivir-resistant virus with the Arg292Lys mutation in two patients among 14 adults infected with A(H7N9), treated initially with oseltamivir, starting at a median 5 days (range 2–10 days) following illness onset. Resistant virus emerged in two of the most severe cases, including one who was treated within 2 days of illness onset, and was associated with persistent or resurgent virus detection and poor outcomes. By contrast, no virus with this mutation was detected in a patient who died after 6 days of therapy, or in the remaining 11 patients