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Coronavirus: need for a therapeutic approach

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For the ISARIC/WHO protocol see http://www.prognosis.org/isaric/

Between March and July, 2003, a global outbreak of severe acute respiratory syndrome (SARS) caused more than 8000 probable or confirmed cases and 774 deaths in 25 countries across five continents.[1] During this outbreak, international cooperation enabled the rapid identification of the SARS-coronavirus (SARS-CoV) and dissemination of information through fast-track publication. However, even after 8000 cases a common therapeutic approach has not been established, and in-vivo evidence remains inconclusive for almost all drugs investigated.[2] In June, 2012, Zaki and colleagues[3] reported for the first time a case of infection with Middle East respiratory syndrome coronavirus (MERS-CoV) in a 60-year-old man, with rapid, progressive pneumonia leading to acute respiratory distress syndrome. Other documented cases,[4-6] and our own findings,[7] show a continuous evolution from pneumonia to respiratory failure and acute respiratory distress syndrome.

In *The Lancet Infectious Diseases*, Drosten and colleagues[8] report the case of a 73-year-old man admitted for respiratory distress. He rapidly developed renal failure and died 10 days after admission as a result of septic shock and multiple organ failure. This study provides a quantitative analysis of viral shedding over time and adds to our knowledge of the natural history of this new virus. The data show the value of samples from the lower respiratory tract compared with samples from the upper respiratory tract for diagnostics, as previously suggested.[8] Viral load in the lower respiratory tract decreases over time, but whether this decrease is linked to the development of a specific antibody response is unknown. The investigators report consistent detection of MERS-CoV in stool on days 12 and 16, but at very low concentrations by contrast with faecal shedding of SARS-CoV.[1] The potential value of stool samples taken early in the course of disease is unknown; stool samples should be collected for the investigation of MERS-CoV, especially when patients present with diarrhoea at onset.[5,7] Of interest is the detection of low concentrations of MERS-CoV in urine at the time the patient developed renal failure, a feature reported in several patients with MERS.[3,5,7] The researchers suggest that the kidneys might be primary targets for MERS-CoV, although high viral loads in urine would have been expected. An alternative hypothesis is that the presence of small amounts of virus in urine[8] and blood[7] could be a hallmark of systemic viral spread, and potentially a marker of disease severity and poor prognosis. The rapid progression of MERS towards septic shock, multiorgan failure, and death in this patient is consistent with this hypothesis.

Although based on few sequences, the phylogenetic analysis provided in the report by Drosten and colleagues dates the time of the common ancestor to mid-2011 (ie, about 1 year before the earliest confirmed cases in Jordan), which suggests that the virus could have spread unnoticed in that time. Furthermore, the analysis suggests geographical clustering of viruses in eastern (Qatar, United Arab Emirates) and western (Jordan, Saudi Arabia) parts of the Arabian Peninsula, which could reflect either repeated introductions or distinct, sustained lineages of human-to-human transmission.

On the basis of the timeline of SARS, the MERS outbreak could still be in the early phase. Now is the time to design and assess therapeutic protocols. Drosten and colleagues provide valuable data for the pathophysiology of MERS-CoV infection; the evolution shown for viral load could provide a timeframe for therapy. From the cases described in the scientific literature the observation of a worsening of respiratory status, from influenza-like symptoms to pneumonia and then acute respiratory distress syndrome, hints at a potential window for treatment. SARS treatment protocols could be used, but the major differences in host responses[9] and susceptibility to drugs such as interferon-alfa[10] for these two coronaviruses should be kept in mind.[8] Interferon with or without ribavirin is a promising candidate treatment.[10,11] Other options are under investigation, such as inhibition of the main protease,[12] convalescent plasma,[13] or monoclonal antibodies. The research community should learn from SARS and use these data to keep one step ahead of the outbreak. A single international therapeutic protocol, building on the generic ISARIC/WHO protocol for severe acute respiratory infections, is needed to identify effective intervention strategies.

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Is MERS another SARS?

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In September, 2012, two fatal cases of a novel coronavirus (CoV) infection were reported: a Saudi patient who was diagnosed in Saudi Arabia, and a Qatari patient who was diagnosed in the UK.[1,2] Symptoms of this transmissible respiratory disease—known as Middle East respiratory syndrome (MERS)—are severe. In *The Lancet Infectious Diseases*, Abdullah Assiri and colleagues[3] provide a clinical synopsis of 47 cases of MERS-CoV infection identified between September, 2012, and June, 2013, in Saudi Arabia. This work enables us to compare MERS with severe acute respiratory syndrome (SARS), at least from a clinical perspective.

Almost all individuals with MERS-CoV infection had fever as the main symptom on admission. However, occurrence of fever is not surprising in (mostly) self-reporting patients; in studies of the clinical features of SARS, with a few exceptions, equivalent selection biases were noted.[4,5] Furthermore, similar to SARS, only a few people with MERS had upper-respiratory-tract symptoms such as sore throat and rhinorrhoea, providing a means to discriminate MERS from the common cold in adults.

A striking difference to SARS is the high rate of underlying comorbidity in patients with MERS. A virus not yet fully adapted to human infection might be more likely to cause illness in people weakened by pre-existing disease. However, caution is necessary when interpreting comorbidity data, because we should compare rates in affected patients with those in the exposed population. In a study of more than 6000 adults attending an outpatient department in Riyadh, 30% had diabetes overall, including 63% of those older than 50 years.[6] In Assiri and colleagues' report, 32 (68%) of 47 patients (most of whom were older than 50 years) had diabetes, a prevalence that does not seem high in view of the background rate. Furthermore, about half the patients included were from an outbreak centred around a haemodialysis unit.[7] The rates of chronic kidney disease (49%) and hypertension (34%) noted would, therefore, be expected in this overall context. Since community-based studies are unavailable for comparison, we have no reason to regard MERS as a disease restricted to people with underlying disorders.

An unfortunate finding from Assiri and colleagues' study is the rapid progression to respiratory failure and intubation in individuals with MERS, occurring about 1 week after onset of symptoms, up to 5 days earlier than in SARS.[5] This finding accords with the high rate of haemoptysis seen in patients with MERS, suggesting severe lung injury. Data of a preliminary infection study in lung explants indeed indicate that MERS-CoV reaches higher replication levels and shows broader cell tropism in the lower human respiratory tract than does SARS-CoV.[8] Even capillary endothelial cells of the lung became infected. Post-mortem analyses and further experimental studies are needed to understand why