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## MERS, SARS and other coronaviruses as causes of pneumonia

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### ABSTRACT

**Human coronaviruses (HCoVs) have been considered to be relatively harmless respiratory pathogens in the past. However, after the outbreak of the severe acute respiratory syndrome (SARS) and emergence of the Middle East respiratory syndrome (MERS), HCoVs have received worldwide attention as important pathogens in respiratory tract infection. This review focuses on the epidemiology, pathogenesis and clinical characteristics among SARS-coronaviruses (CoV), MERS-CoV and other HCoV infections.**

**Key words:** human coronaviruses, Middle East respiratory syndrome, pneumonia, severe acute respiratory syndrome.

**Abbreviations:** AKI, acute kidney injury; CAP, community-acquired pneumonia; CK, creatinine kinase; CoV, coronavirus; DPP-4, dipeptidyl peptidase 4; HCoV, human coronavirus; ICU, intensive care unit; IFN, interferon; ISG, IFN-stimulated gene; MERS, Middle East respiratory syndrome; MPA, mycophenolic acid; RT-PCR, reverse transcription polymerase chain reaction; SARS, severe acute respiratory syndrome; WHO, World Health Organization.

### INTRODUCTION

Coronaviruses (CoVs), a large family of single-stranded RNA viruses, can infect a wide variety of animals, including humans, causing respiratory, enteric, hepatic and neurological diseases.<sup>1</sup> As the largest known RNA viruses, CoVs are further divided into four genera: alpha-, beta-, gamma- and delta-coronavirus. In humans, CoVs cause mainly respiratory tract infections. Currently, six human coronaviruses (HCoVs) have been identified. These include the alpha-CoVs HCoV-NL63 and HCoV-229E and the beta-CoVs HCoV-OC43, HCoV-HKU1, severe acute respiratory syndrome-CoV

(SARS-CoV),<sup>2</sup> and Middle East respiratory syndrome-CoV (MERS-CoV).<sup>3</sup>

Although HCoVs have been identified for decades, their clinical importance and epidemic possibility was not recognized until the outbreak of SARS and MERS.<sup>2,3</sup> In 2002, the SARS epidemic originated from an animal market in South China and then affected more than 8000 people, with 916 deaths in 29 countries.<sup>4</sup> Subsequently, the World Health Organization (WHO) was notified of 2066 laboratory-confirmed cases of MERS-CoV infection, with at least 720 deaths between 2012 and 17 August 2017.<sup>5</sup> While found in 27 countries, more than 80% of illnesses were reported from Saudi Arabia.

This article will review the epidemiology, pathogenesis, clinical characteristics and management of patients with HCoVs infection.

### EPIDEMIOLOGY

#### Origin of HCOVs

Although CoVs are estimated to have circulated on earth for centuries,<sup>6,7</sup> the origin of CoVs remains obscure. At the beginning of the outbreak of SARS and MERS, palm civets<sup>8</sup> and dromedary camels,<sup>9</sup> respectively, were suggested to be the natural reservoir of these two HCoVs. But further virologic and genetic studies indicate that bats are reservoir hosts of both SARS-CoV<sup>10</sup> and MERS-CoV,<sup>11</sup> which then use palm civets and dromedary camels as intermediary host before dissemination to humans. Recent studies further propose that bat CoVs are the gene source of most alpha-CoVs and beta-CoVs, whereas avian CoVs are considered the gene source of most gamma- and delta-CoVs.<sup>6,12</sup> Meanwhile, rodents are proposed to be the reservoir for ancestors of lineage A beta-CoVs which include HCoV-HKU1 and HCoV-OC43.<sup>13</sup>

#### Transmission from animal to human

The mechanism and route of transmission of SARS-CoV and MERS-CoV remains elusive. Direct contact with intermediary host animals or consumption of milk, urine, or uncooked meat were hypothesized to be

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the main routes of SARS-CoV and MERS-CoV transmission.

### Transmission from human to human

Human-to-human transmission of SARS-CoV and MERS-CoV occurs mainly through nosocomial transmission. From 43.5–100% of MERS patients in individual outbreaks were linked to hospitals,<sup>14,15</sup> which was similar in SARS patients.<sup>16</sup> A study from the Republic of Korea revealed that index patients who transmitted to others had more non-isolated days in the hospital, body temperature of  $\geq 38.5^{\circ}\text{C}$  and pulmonary infiltration of  $\geq 3$  lung zones.<sup>17</sup> Transmission between family members occurred in only 13–21% of MERS cases and 22–39% of SARS cases.<sup>17</sup> Another Korean study suggested that transmission of MERS from an asymptomatic patient is rare.<sup>18</sup> In contrast to SARS-CoV and MERS-CoV, direct human-to-human transmission was not reported for the other four HCoVs.<sup>19</sup>

### Clinical epidemiology

The SARS epidemic originated from an animal market in Guangdong Province of China and subsequently spread to 29 countries. No large outbreaks have been reported in other areas after the initial epidemic. Nosocomial acquisition was very important for SARS as health care workers comprised 22% of reported cases in China and >40% in Canada.<sup>20</sup>

A large majority of MERS cases have occurred in the Arabian Peninsula.<sup>21,22</sup> A case-control study comparing 30 MERS patients to 116 controls in Saudi Arabia found direct contact with dromedaries in the 2 weeks before illness onset was associated with MERS-HCoV illness.<sup>23</sup> Outbreaks in other countries all resulted from index cases with travel history to the Middle East or North Africa.<sup>24,25</sup>

The other HCoVs have a global distribution and are mainly transmitted in a seasonal endemic way,<sup>26</sup> usually peaking in winter and spring, with a few cases occurred in early summer.<sup>27,28</sup> Epidemic studies of community-acquired pneumonia (CAP) revealed that the four non-SARS, non-MERS HCoVs accounted for 0.6–2.5% of adult CAP patients.<sup>19,29–31</sup>

## PATHOGENESIS

Current understanding of the pathogenesis of HCoVs infection is still limited. However, several significant differences in the pathogenesis exist among SARS-CoV, MERS-CoV and the other HCoVs.

### Cell entry and receptors

The critical first step for HCoV infection is entry into the susceptible host cells by combining with a specific receptor. Spike proteins (S proteins) of HCoVs are a surface-located trimeric glycoprotein consisting of two subunits: the N-terminal S1 subunit and the C-terminal S2 subunit. The S1 subunit specializes in recognizing and binding to the host cell receptor while the S2 region is responsible for membrane fusion.<sup>32</sup> To date, a wide range of diverse cellular receptors specifically

recognized by the S1 domains have been identified for all HCoVs except HCoV-HKU1 (Table 1).

ACE2, the receptor for SARS-CoV and HCoV-NL63,<sup>1,33,34</sup> is a surface molecule localized on arterial and venous endothelial cells, arterial smooth muscle cells, epithelia of the small intestine and the respiratory tract. In the respiratory tract, ACE2 is expressed on the epithelial cells of alveoli, trachea, and bronchi, bronchial serous glands, and alveolar monocytes and macrophages. ACE2 is a homologue of the ACE protein, and both are key enzymes of the renin-angiotensin system.<sup>35</sup> ACE2 plays a protective role in lung failure and its counterpart ACE promoting lung oedema and impaired lung function.<sup>36</sup> Downregulation of ACE2, as occurs during SARS-CoV infection, is believed to contribute to pathological changes in the lung.<sup>35,37</sup> This form of lung damage can be attenuated by blocking the renin-angiotensin pathway.<sup>37</sup> Interestingly, HCoV-NL63 also employs the SARS receptor for cellular entry,<sup>34</sup> despite their markedly different pathogenicity and disease courses. This finding suggests that receptor usage may not be the only factor that determines the severity of HCoV infection.

Dipeptidyl peptidase 4 (DPP4, also known as CD26), the receptor for MERS-CoV,<sup>38</sup> is a multifunctional cell-surface protein widely expressed on epithelial cells in kidney, small intestine, liver and prostate and on activated leukocytes. DPP4 is expressed in the upper respiratory tract epithelium of camels.<sup>39</sup> In the human respiratory tract, DPP4 is mainly expressed in alveoli rather than the nasal cavity or conducting airways.<sup>38</sup> DPP4 is a key factor in the activation of T cells and immune response costimulatory signals in T cells, which could indicate a possible manipulation of the host immune system.<sup>40</sup>

Human aminopeptidase N (CD13), a cell-surface metalloprotease on intestinal, lung and kidney epithelial cells, has been identified as the receptor for hCoV-229E.<sup>41</sup> The receptor for HCoV-OC43 is 9-O-acetylated sialic acid. Currently, the receptor for HCoV-HKU1 has not been identified.

### Interferon and interferon-stimulated genes

The interferon (IFN) family of cytokines, including IFN- $\alpha$ , IFN- $\beta$  and IFN- $\gamma$ , provide the first line of defence against viral pathogens. They initiate transcription of hundreds of IFN-stimulated genes (ISGs) that have antiviral, immune modulatory and cell regulatory functions.

Delayed recognition is critical for HCoVs to survive and replicate in the host. In vitro studies showed that both SARS-CoV and MERS-CoV have evolved genetic mechanisms to delay IFN induction and dysregulate ISG effector functions in primary human airway epithelial cells or in cultured cells.<sup>42,43</sup> Menachery *et al.* found SARS-CoV infection could result in IFN- $\alpha$  induction only after 12 h in cultured Calu3 cells, with IFN- $\beta$ 5 and IFN- $\gamma$ 1 induction even further delayed.<sup>42</sup> Similar to SARS-CoV, MERS-CoV also fails to induce IFNs prior to 12 h, with the exception of IFN- $\alpha$ 5. Lau *et al.* serially measured mRNA levels of eight cytokine genes up to 30 h post-infection in Calu-3 cells infected with MERS-CoV and SARS-CoV.<sup>43</sup> Calu-3 cells infected by MERS-

**Table 1** Biological characteristic of SARS-CoV, MERS-CoV and other HCoVs

	SARS-CoV	MERS-CoV	HCoV-229E	HCoV-NL63	HCoV-OC43	HCoV-HKU1
Genus	Beta-CoVs lineage B	Beta-CoVs, lineage C	Alpha-CoVs	Alpha-CoVs	Beta-CoVs, lineage A	Beta-CoVs, lineage A
Intermediary host	Palm civet	Dromedary, camel	Not defined	Not defined	Not defined	Not defined
Receptor	ACE2	Dipeptidyl peptidase 4 (DPP4 or CD26)	Human aminopeptidase N (CD13)	ACE2	9-O-Acetylated sialic acid	Not identified
Receptor distribution	Arterial and venous endothelium; arterial smooth muscle; small intestine, respiratory tract epithelium; alveolar monocytes and macrophages	Respiratory tract epithelium; kidney, small intestine; liver and prostate; activated leukocytes	Monocytic and granulocytic lineage; synaptic membranes of the central nervous system; intestinal, lung and kidney epithelial cells	Same as SARS-CoV	Sub-maxillary mucin	
Susceptibility in human cell lines in vitro	Respiratory tract; kidney; liver	Respiratory tract; intestinal tract; genitourinary tract; liver, kidney, neurons; monocyte; T lymphocyte; and histiocytic cell lines	Liver, primary embryonic lung fibroblasts, neural tissue, monocytes, dendritic cells and macrophages	Intestinal tract; kidney	Intestinal tract; neural tissue	Ciliated airway epithelial

ACE2, angiotensin-converting enzyme 2; CoV, coronavirus; HCoV, human coronavirus; MERS, Middle East respiratory syndrome; SARS, severe acute respiratory syndrome.

CoV showed marked induction of the proinflammatory cytokines IL-1 $\beta$ , IL-6 and IL-8 at 30 h but lack of production of the innate antiviral cytokines tumour necrosis factor (TNF)- $\alpha$ , IFN- $\beta$  and IFN- $\gamma$ -induced protein-10, compared with SARS-CoV. These data suggest that MERS-CoV attenuates innate immunity and induces a delayed proinflammatory response in human lung epithelial cells, which correlates with disease severity and clinical course.

To date, no evidence exists that the other HCoVs have the ability to inhibit IFN production or regulate ISG expression. This decreased ability to escape from the innate immune responses of the host may explain the generally milder clinical disease associated with HCoV infection with these genera.

### Cell line tropism

The differential cell line susceptibility, species tropism and viral replication efficiency of HCoVs correlate with clinical and epidemiologic characteristics. Compared with SARS-CoV and other HCoVs, MERS-CoV has a much broader cell line tropism (Table 1). Chan and colleagues tested cell line susceptibility of MERS-CoV in 15 human cell lines and found significantly increased mean viral loads in 11 after infection, including lower airway (A549, Calu-3 and HFL), intestinal tract (Caco-2), liver (Huh-7), kidney (HEK), neuronal (NT2), monocyte (THP-1 and U937), T lymphocyte (H9) and histiocyte (His-1) cell lines.<sup>44</sup> Respiratory, intestinal, liver, kidney and histiocyte cell lines also

showed viral nucleoprotein expression by immunofluorescence, in addition to a high viral load. MERS-CoV could induce cytopathic effects as early as day 1 in the intestinal and liver cell lines and on day 3 in the lower respiratory tract cell lines, faster than those induced by SARS-CoV.<sup>45,46</sup> These findings could partly explain the apparently more severe clinical presentations and higher fatality rate in MERS patients.

### DIAGNOSIS

Diagnosis of SARS and MERS is based on a comprehensive contact and travel history and precise laboratory tests. Current diagnostic tools include molecular methods, serology and viral culture.<sup>27,47</sup> The most common diagnostic method is molecular detection such as RT (reverse transcription)-PCR or real-time RT-PCR using RNA extracted from respiratory tract samples,<sup>27</sup> such as nasopharyngeal swab, sputum, deep tracheal aspirate or bronchoalveolar lavage. Notably, lower respiratory tract samples usually yield significantly higher viral loads and genome fractions than upper respiratory tract samples,<sup>48</sup> consistent with the tissue tropism.

Sensitivity of antibody detection is usually lower than molecular methods and mostly used in retrospective diagnosis. For antibody detection, an interval of 14–21 days between acute and convalescent serum samples is required in order to document seroconversion of at least a four-fold rise of the antibody titres. If

only a single sample can be collected, at least 14 days after the onset of symptoms is required for validity. Serology can be considered when virology testing by RT-PCR is limited or the infection is considered late in the course of the illness (>14 days).<sup>47</sup>

Viral culture is relatively time and labour consuming. Culture is much more useful in the initial phase of emerging epidemics before other diagnostic assays are clinically available. Furthermore, viral culture can also be employed in *in vitro* and *in vivo* antiviral and vaccine evaluation studies.<sup>49</sup> Antigen detection assay is another potential diagnostic tool to confirm SARS-CoV and MERS-CoV infection but is not recommended by current WHO guidelines.<sup>47</sup>

## CLINICAL CHARACTERISTICS

### Demographic and clinical features

Both SARS and MERS present with a spectrum of disease severity ranging from flu-like symptoms to acute respiratory distress syndrome (ARDS). Clinical characteristics comparing SARS and MERS patients are seen in Table 2.

Age and underlying disease are significant independent predictors of various adverse outcomes in SARS.<sup>50</sup> SARS cases were mainly seen in young healthy individuals; whereas half of the cases of MERS-CoV infection occurred in individuals older than 50 years.<sup>21</sup> Compared with SARS patients, pre-existing chronic illnesses, such as diabetes (31%), hypertension (33%), chronic renal failure (15%), chronic heart disease (15%) and chronic pulmonary disease (13%), were more frequent in MERS patients. Clinical symptoms on admission included fever, cough, myalgia and shortness of breath in both SARS and MERS patients, while symptoms of upper respiratory tract infection such as sore throat were also frequent. Atypical symptoms such as diarrhoea and vomiting developed in both SARS and MERS patients.

The other HCoVs infect people of all age groups seasonally and cause severe lower respiratory tract infection primarily in frail patients, such as neonates and the elderly.<sup>51</sup> Chronic underlying disease, immunosuppression and extremes of age increase the risk of severe HCoV infections and associated death rate.<sup>19,51,52</sup>

## LABORATORY FINDINGS

### Kidney impairment

Acute kidney injury (AKI) is a significant characteristic of both SARS and MERS patients. One study reported that 6.7% of SARS patients had acute renal impairment and 84.6% had proteinuria.<sup>53</sup> AKI is much more common in MERS patients, occurring in up to 43%.<sup>54</sup>

The mechanism of the high AKI incidence in both SARS and MERS patients is not well clarified. Pre-existing co-morbid conditions and direct viral involvement of the kidneys<sup>62,63</sup> may contribute to development of AKI.<sup>53,54</sup> Since ACE2 and DPP4, the receptors for SARS-CoV and MERS-CoV, are expressed at high levels in the kidney, functional impairment of these cell receptors by viral binding may contribute to the risk of

**Table 2** Demographic and clinical features of MERS-CoV and SARS-CoV infection

Clinical and epidemiologic aspects	SARS <i>n</i> = 357 (%)	MERS <i>n</i> = 245 (%)
Health care workers	142 (40%)	42 (17%)
Male	158 (44%)	154 (63%)
Co-morbidities		
Diabetes	21 (5.9%)	75 (31%)
Malignancy	9 (2.5%)	27 (11%)
Chronic pulmonary diseases (including COPD and asthma)	5 (1.4%)	32 (13%)
Chronic renal failure	2 (0.1%)	37 (15%)
Chronic heart disease	24 (6.7%)	37 (15%)
Chronic liver diseases (including chronic hepatitis B)	12 (3.4%)	10 (4.1%)
Hypertension	Not mentioned	81 (33%)
Others	6 (1.7%)	13 (5.3%)
Symptoms on admission		
Fever	356 (99%)	206 (84%)
Headache	139 (39%)	46 (19%)
Myalgia	211 (59%)	98 (40%)
Cough	208 (58%)	155 (63%)
Shortness of breath	95 (27%)	86 (35%)
Sore throat	61 (17%)	33 (13%)
Nausea/vomiting	55 (15%)	37 (15%)
Diarrhoea	62 (17%)	50 (20%)
Clinical outcome		
Invasive mechanical ventilation	<b>59 (17%)</b>	<b>91(37%)</b>
Death	<b>18 (5.0%)</b>	<b>71 (29%)</b>

CoV, coronavirus; MERS, Middle East respiratory syndrome; SARS, severe acute respiratory syndrome.

AKI. Elevated creatinine kinase (CK) values (176–1466 U/L) observed in 36% of SARS patients suggests rhabdomyolysis may also contribute.<sup>55</sup>

### Cardiovascular manifestations

A cardinal difference between MERS and SARS is the frequency of cardiovascular involvement. Despite the high lethality, shock was distinctly unusual in SARS until late stages when hypotension likely resulted from bacterial superinfections.<sup>56–58</sup> In contrast, need for vasopressor therapy was much more common in MERS,<sup>50,58</sup> up to 81% in one series.<sup>58</sup> Need for vasopressors was an independent risk factor for death in the intensive care unit (ICU) (odds ratio = 18.3, 95% confidence interval: 1.1–302.1, *P* = 0.04).<sup>58</sup> Multi-organ involvement was seldom reported with the endemic HCoV infections,<sup>19</sup> despite occasional fatal pneumonia in highly immunocompromised patients.

### Other manifestations

Haematological abnormalities such as thrombocytopenia and lymphopenia were common in both SARS<sup>55,56</sup> and MERS patients.<sup>21,22</sup> Thrombocytopenia and lymphopenia may be predictive of fatal outcome in MERS-CoV patients.<sup>22</sup> Other laboratory findings included

elevated CK, lactate dehydrogenase, alanine aminotransferase and aspartate aminotransferase levels.

## RADIOLOGICAL

Air-space opacities are the main radiographical feature in SARS patients.<sup>56,59</sup> In one retrospective study, initial chest radiographs were abnormal in 108 of 138 (78.3%) of SARS patients and all showed air-space opacities.<sup>59</sup> Of these 108 patients, 59 had unilateral focal involvement while 49 had either unilateral multifocal or bilateral involvement. Lower lung zone (64.8%) and right lung (75.9%) were more commonly involved. Four patterns of radiographical progression were recognized in those patients: type 1) initial radiographical deterioration to peak level followed by radiographical improvement occurred in the majority (97 of 138 patients, 70.3%); type 2) fluctuating radiographical changes were seen in 24 patients (17.4%); type 3) static radiographical appearance in 10 patients (7.3%); and type 4) progressive radiographic deterioration in 7 patients (5.1%). In contrast, the most common radiographical features in MERS patients were ground-glass opacities and consolidation.<sup>60,61</sup> Das *et al.* reported that ground-glass opacity was the most common abnormality (66%) in 55 MERS patients, followed by consolidation (18%).<sup>61</sup> Meanwhile, type 2 radiographical progression (20 patients) was most common in those MERS patients, followed by type 4 (14 patients) and type 3 (7 patients). Type 1 radiographical progression was observed only in four patients. Pleural effusion ( $P = 0.001$ ), pneumothorax ( $P = 0.001$ ) and type 4 radiographical progression ( $P = 0.001$ ) were more frequent in MERS patients who died compared with recovered patients. Similar to the radiographical findings, computed tomography findings in MERS patients also included ground-glass opacity (53%), consolidation (20%) or a combination of both (33%).<sup>62</sup> Pleural effusion was noted in 33% of cases and was associated with a poor prognosis for MERS-CoV infection.<sup>61</sup>

## OUTCOME

As shown in Table 2, more MERS cases progressed to respiratory failure and received invasive mechanical ventilation therapy than SARS patients. The occurrence of AKI<sup>22,54</sup> and the usage of vasopressor therapy were also more frequent in MERS patients in comparison with SARS.<sup>53,58</sup> In a retrospective analysis, vasopressor therapy was proposed to be an independent risk factor for death in the ICU.<sup>58</sup>

MERS demonstrated a higher case fatality rate than SARS. Differences in host factors, such as age and underlying diseases,<sup>50,60</sup> may explain some differences. However, the differential cell line susceptibility, viral replication efficiency, ability to inhibit IFN production and receptor characteristics may also be responsible for the difference in the outcome of SARS-CoV and MERS-CoV infection.<sup>43,44</sup>

Compared with SARS and MERS, other HCoV-associated pneumonia cases usually have relatively mild symptoms and recovered quickly.<sup>19</sup> Fatal cases

**Table 3** Comparison of the susceptibility of MERS-CoV and SARS-CoV with different antiviral agents

Antiviral agents	Viruses	Tested cell line	EC50 values
Ribavirin	SARS-CoV	Caco2 cells	$4.7 \pm 2.6(0.3 \pm 0.12$ if ribavirin and IFN- $\beta$ combined)
Interferon- $\beta$	SARS-CoV	Caco2 cells	$28 \pm 7 (0.6 \pm 0.27$ if ribavirin and IFN- $\beta$ combined)
Ribavirin	MERS-CoV	Vero cells	$9.99 \pm 2.97$
Intron A (recombinant interferon- $\alpha$ 2b)	MERS-CoV	Vero cells	$6709.79 \pm 1747.97$
Avonex (recombinant interferon- $\beta$ 1a)	MERS-CoV	Vero cells	$5073.33 \pm 7333.86$
Betaferon (recombinant interferon- $\beta$ 1b)	MERS-CoV	Vero cells	$17.64 \pm 1.09$
Mycophenolic acid	MERS-CoV	Vero cells	$0.17 \pm 0.03$

CoV, coronavirus; EC50, 50% effective cytotoxic concentration; IFN, interferon; MERS, Middle East respiratory syndrome; SARS, severe acute respiratory syndrome.

were reported mainly in frail patients, such as neonates, the elderly and immunocompromised patients.

## TREATMENT

At the moment, no specific therapy for SARS-CoV, MERS-CoV and the other HCoVs infection is available. Symptomatic and supportive treatment is the mainstay of therapy for patients infected by HCoVs.

A number of agents show effectiveness in vitro and/or in animal models and may improve the outcome in patients (Table 3). Currently, the most commonly prescribed antiviral regimens in the clinical settings are ribavirin, IFNs and lopinavir/ritonavir.

To date, ribavirin and ribavirin plus various types of IFN have been the most common therapeutic interventions tried in patients with SARS and MERS.<sup>63-65</sup> Ribavirin, a nucleoside analogue, has a wide spectrum of antiviral activity by inhibiting viral RNA synthesis and mRNA capping.<sup>66</sup> When used alone for treatment of SARS, the clinical effect was inconsistent. Although in vitro studies show that combination with IFN- $\beta$  will give both these agents better antiviral activity, the clinical effect remains controversial.

IFNs are important for host defence against viruses. In in vitro experiments, IFN products were effective in inhibiting both SARS-CoV and MERS-CoV, with best antiviral activity seen with IFN- $\beta$ 1b (Table 3).<sup>63,67</sup> Previous studies had shown a positive impact of various IFNs on aspects of treatment of SARS and MERS patients, such as a better oxygen saturation and rapid

resolution of inflammation, but no effect on more significant outcomes like hospital stay and long-term survival.<sup>64,65,68</sup>

Lopinavir and ritonavir are protease inhibitors that may inhibit the 3C-like protease of MERS-CoV and modulate apoptosis in human cells. Addition of lopinavir/ritonavir to ribavirin was associated with improved clinical outcome compared with ribavirin alone in SARS patients.<sup>69</sup> Although lopinavir only showed sub-optimal 50% effective cytotoxic concentration (EC50) against MERS-CoV in vitro,<sup>67</sup> lopinavir/ritonavir experimental therapy was proved to improve the outcome of MERS-CoV infection in animal model.<sup>70</sup>

Mycophenolic acid (MPA) is another potential therapeutic choice. Frequently used as an immunosuppressant drug to prevent rejection in organ transplantation by inhibiting lymphocyte proliferation, MPA also prevents replication of viral RNA. *in vitro* studies showed that MPA had strong inhibition activity against MERS-CoV.<sup>71</sup> However, use in a non-human primate model showed that all MPA-treated animals developed severe and/or fatal disease with higher mean viral loads than the untreated animals.<sup>70</sup>

Passive immunotherapy using convalescent phase human plasma was also used in the treatment of SARS and MERS. An exploratory meta-analysis found that convalescent plasma decreased mortality in SARS-CoV patients only if administered within 14 days of illness.<sup>72</sup> A network for the use of convalescent plasma in the treatment of MERS cases is currently being formed to test its safety, efficacy and feasibility.<sup>73</sup>

Corticosteroids were used extensively during the SARS outbreak, generally in combination with ribavirin. Lessons from SARS showed that corticosteroid treatment was associated with a higher subsequent plasma viral load<sup>74</sup> with increased complications.

A variety of other agents, including antiviral peptides, monoclonal antibodies, cell or viral protease inhibitors antivirals, are shown to be effective *in vitro* and/or in animal models.<sup>75-78</sup> Clinical trials of these agents are awaited.

## SUMMARY

The pandemic potential of HCoV remains a threat for public health and active surveillance is prudent. As no specific treatment is currently available for HCoV, further research into the pathogenesis of the HCoV infection in order to find appropriate targets for treatment is needed. In immunosuppressed pneumonia patients, non-SARS, non-MERS HCoV should be included in the differential diagnosis.

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