Journal of Intensive Care Medicine
1-5

DOI: 10.1177/0885066615579858
jic.sagepub.com
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Characteristics and Outcomes of Middle East Respiratory Syndrome Coronavirus Patients Admitted to an Intensive Care Unit in Jeddah, Saudi Arabia

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Abstract

Background: An increasing number of patients are being infected with Middle East respiratory syndrome coronavirus (MERS-CoV) since the first case was identified in September 2012. We report the characteristics and outcomes of MERS-CoV–confirmed patients who developed critical illness requiring admission to an intensive care unit (ICU). **Methods:** We conducted a prospective cohort study of all MERS-CoV–confirmed cases who were admitted to our ICU from March 20, 2014, till June 1, 2014. Presenting symptoms, comorbid conditions, and details of their ICU stay were recorded. **Results:** Eight patients were admitted to the ICU with MERS-CoV infection. All had signs of respiratory distress with 7 requiring mechanical ventilation. Three patients were health care workers. In all, 6 patients had comorbid conditions and 5 patients developed multiorgan system failure (MOSF). In all, 5 patients expired, 2 were discharged alive, and 1 remained intubated at the end of the study period. **Conclusions:** Middle East respiratory syndrome coronavirus carries a high mortality rate in patients who require ICU admission, with a significant number of patients developing MOSF. Further investigation is needed to determine optimal management guidelines for these patients.

Keywords

Middle East respiratory syndrome coronavirus, respiratory failure, intensive care

Introduction

Middle East respiratory syndrome coronavirus (MERS-CoV) was first isolated in humans in September 2012 in Saudi Arabia.[1] Since then a number of cases with MERS-CoV have been reported, with human-to-human and camel-to-human transmission.[2,3] However, there is little published information on the outcomes of infected patients who develop critical illness requiring intensive care unit (ICU) monitoring. We report the characteristics and outcomes of 8 MERS-CoV–confirmed cases that required ICU admission.

Material and Methods

The study was approved by the institutional review board of National Guard Health Affairs, King Abdullah International Medical Research Center, Jeddah, Saudi Arabia, and given the observational nature of the study consent was not required.

Patients suspected of MERS-CoV infection were tested with real-time polymerase chain reaction (RT-PCR) assay developed by Roche (Berlin, Germany), using nasopharyngeal swabs or tracheal aspirates. Health care workers involved in collecting samples had been trained by the infectious disease physicians on the proper technique of sample collection.

All patients suspected of MERS-CoV infection were also tested for influenza A, B, and H1N1.

Samples were tested at the regional reference laboratory, and positivity was determined if both assays for the upstream

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Received November 4, 2014, and in revised form February 9, 2015.
Accepted for publication February 10, 2015.

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E protein (upE gene) and ORF1a were positive. We define cases based on RT-PCR positivity for MERS-CoV of the respiratory specimens and the requirement of ICU admission.

Data were prospectively collected from the time of admission to the ICU until the patient was discharged from the ICU or expired. This included demographic, clinical, and laboratory variables as well as details of the time course of a patient's illness, microbiological test results, and treatment received. Data for all patients were collected using a standard Microsoft excel spreadsheet (U.S.A), and descriptive statistic analysis applied where appropriate. Variables were collected at time of ICU admission, day 3, day 7, and day 14 of ICU admission as was applicable for individual cases. The study did not receive any external funding.

Results

Four hundred and seventy patients were tested for suspected MERS-CoV infection in our hospital from March 20, 2014, till June 1, 2014. During this time, 8 patients were confirmed to be positive for MERS-CoV. All 8 patients required ICU admission, with 7 requiring intubation. Our patients tended to be middle aged, often with comorbid conditions. Table 1 gives details of the patients as well as their symptoms. It was observed that most patients had been having upper respiratory symptoms with cough and high fevers for less than a week. Diarrhea, which was reported to be associated with MERS-CoV infection before, was only observed in 1 patient in our case series. Six cases were diagnosed by positive tracheal aspirate PCR after the initial nasopharyngeal swab had been negative. Of the 8 patients, 3 were health care workers, one of whom worked in a primary health care clinic, other was a resident physician who acquired the infection at another hospital in the city during an external rotation and the third works as a janitor in our institution. Among the remaining 5 patients, 2 had community acquired infection (without clear exposure risks to infected humans or animals) while 3 had a history of hospitalization within 2 weeks of admission to an outside hospital and therefore may have acquired the infection from a health care facility.

All patients were admitted to the ICU primarily because of respiratory distress. Seven patients required intubation. One patient who was not intubated also initially required oxygen via nonrebreather mask to maintain his saturations above 90%. Noninvasive ventilation was attempted in 5 patients; however, all ended up failing noninvasive ventilation and needed intubation and mechanical ventilation. All patients were noted to have developed acute respiratory distress syndrome (ARDS) with low P/F ratios. Table 2 gives details of ventilatory parameters and arterial blood gases of patients during their ICU course. The median length of mechanical ventilation was 9 days (range 0-53 days). One patient required initiation of extracorporeal membrane oxygenation (ECMO) in order to maintain adequate oxygen delivery. The rest of the patients were managed by the ARDS protocol of low tidal volume ventilation strategy. High frequency oscillation was not available in our hospital and hence was not used in any patient.

Table 1. Basic Characteristics.

Variable	Result, N = 8
Median age (range)	56.5 (26-94)
Male patients (%)	6 (75%)
Median body mass index (range)	28.3 (18.8-37.8)
Median duration of symptoms (range), days	5.5 (3-11)
Percentage with cough	87.5
Percentage with sputum production	75
Percentage with dyspnea	75
Percentage with fever	87.5
Median temperature on admission (range), °C	38.4 (36.3-39.5)
Median peak temperature during first 3 days of ICU admission (range), °C	38.7 (36.9-39.5)
Percentage with myalgia	62.5
Percentage with diarrhea	25
Percentage with chest pain	25
Percentage with altered mental status	12.5
Percentage with headache	12.5
Comorbid conditions	
Diabetes mellitus	62.5%
Hypertension	50%
Congestive heart failure or ischemic heart disease	37.5%
Cirrhosis	12.5%
G-6-PD deficiency	12.5%
Result of initial nasophargyngeal swab for MERS-CoV	
Positive	2
Negative	6
Result of initial tracheal aspirate specimen for MERS-CoV	
Positive	7
Negative	0

Abbreviations: G-6-PD, glucose-6-phosphate dehydrogenase deficiency; ICU, intensive care unit; MERS-CoV, Middle East respiratory syndrome coronavirus.

We noted that all patients upon presentation to the ICU had lymphopenia, although anemia or thrombocytopenia was not observed (see Table 3 for details of laboratory variables). Coagulopathy, impairment of liver, or kidney function was not observed earlier in the ICU course; however, 5 patients did develop multiorgan system failure (MOSF) during the course of their ICU stay. All 8 patients demonstrated elevation in creatinine kinase (CK) levels during their ICU admission (see Table 3).

Two patients with a history of congestive heart failure presented to the ICU in cardiogenic shock along with respiratory distress. In both cases, bedside transthoracic echocardiograms revealed global hypokinesia with reduction in ejection fraction. Two other patients developed myocardial infarction during their ICU stay (1 non-ST-segment elevation myocardial infarction and 1 ST-segment elevation myocardial infarction). One patient developed right-sided segmental pulmonary embolism. All 5 patients progressed to MOSF and expired, despite receiving intensive supportive care. The ECMO was only feasible in 1 patient, mentioned previously, who ultimately survived. The nonsurvivors were

Table 2. Respiratory and Hemodynamic Parameter During Intensive Care Unit (ICU) Stay.

Variable	Day 1 of ICU, N = 8	Day 3 of ICU, N = 7	Day 7 of ICU, N = 6	Day 14 of ICU, N = 3
Patients on mechanical ventilation	5	5	6	3
Median APACHE II score (range)	13 (5-30)	16.5 (15-30)	16.5 (15-34)	15.5 (15-16)
Median Fio_2 (range), %	95 (35-100)	57.5 (35-100)	55 (35-100)	45 (40-60)
Median tidal volume (range), mL	500 (360-500)	450 (310-650)	425 (250-550)	500 (250-550)
Median PEEP (range), cm H_2O	9 (5-12)	9 (5-16)	8.5 (5-18)	10 (7-12)
Median peak airway pressure (range), cm H_2O	32 (29-40)	33 (25-37)	32.5 (21-57)	25 (12-28)
Median respiratory rate (range), breaths/min	24 (14-40)	24 (10-36)	29.5 (14-35)	12 (12-22)
Median Pao_2/Fio_2 ratio (range)	148 (47-283)	203 (47-214)	136 (54-237)	171 (112-210)
Median pH (range)	7.33 (7.19-7.45)	7.37 (7.3-7.49)	7.42 (6.9-7.49)	7.4 (7.37-7.5)
Median Pco_2 (range), mm Hg	34.5 (30-50)	34 (28-57)	45.5 (30-63)	46 (44-47)
Median Po_2 (range), mm Hg	86.5 (48-146)	64 (44-103)	67.5 (53-81)	78 (67-85)
Median bicarbonate (range), mEq/L	21.5 (15-25)	22 (15-28)	22.5 (13-36)	28 (26-34)
Median mean arterial blood pressure (range), mm Hg	77.5 (61-97)	79 (72-82)	72 (67-102)	82 (72-82)
Median central venous pressure (range)	12 (6-17.5)	15 (8-16.5)	13.5 (7-16)	10 (6-13)
Median heart rate (range), beats/min	94.5 (58-134)	96 (64-112)	82 (55-110)	84 (60-121)
Median norepinephrine dose (range), μg/min	5 (0-100)	4 (0-50)	8 (0-100)	0 (0-3)

Abbreviations: APACHE II, Acute Physiology and Chronic Health Evaluation II; Fio_2, fraction of inspired oxygen; PEEP, Positive end-expiratory pressure.

Table 3. Laboratory Variables During Intensive Care Unit (ICU) Stay.

Variable (normal values)	Day 1 of ICU	Day 3 of ICU	Day 7 of ICU	Day 14 of ICU
Median lactate, mmol/L (0.70-2.0)	1.86 (0.78-3.96)	3.2 (3.2-3.2)	1.65 (1.65-1.65)	1.71 (1.71-1.71)
Median creatinine, μmol/L (53-97)	84 (72-295)	91 (66-554)	150 (72-292)	73 (60-94)
Median AST, U/L (5-34)	92.5 (39-4202)	92 (44-4202)	116 (95-4202)	104 (96-251)
Median ALT, U/L (5-55)	60.5 (9-7289)	61 (8-5050)	53 (19-698)	46 (39-698)
Median bilirubin, μmol/L (3.4-20.5)	20 (3.7-86)	22.1 (2.8-72)	36 (5.4-99)	42 (8.2-46)
Median hemoglobin, g/dL (11.5-16.5)	12.8 (10-2-15.7)	14 (10.2-14.5)	10.75 (8.5-14.1)	9.7 (9-10)
Median platelets, $\times 10^9$/L (150-450)	179 (37-338)	209 (67-361)	129 (32-307)	163 (41-232)
Median leukocytes, $\times 10^9$/L (11.5-16.5)	4.3 (3.2-22.6)	5.4 (4.4-17.8)	6.85 (0.3-23.3)	11.4 (2.5-12.3)
Median lymphocytes $\times 10^9$/L (1.5-4.0)	0.48 (0.3-1.07)	0.63 (0.39-1.13)	0.54 (0.16-1.09)	0.31 (0.29-0.83)
Median INR (0.8-1.2)	1.1 (0.9-1.4)	1.1 (0.59-1.2)	1.2 (0.57-1.2)	1.2 (1.1-1.2)
Median creatinine kinase, IU/L (29-166)	123.5 (61-6070)	421.5 (135-3203)	647 (71-8745)	305 (197-3955)

Abbreviations: AST, aspartate aminotransferase; ALT, alanine transaminase; INR, international normalized ratio.

considered inappropriate candidates for ECMO, given their advanced age and severe comorbidities.

Another patient who was initially recovering from her respiratory failure unfortunately developed spontaneous intracranial hemorrhage. Computed tomography angiogram of the brain did not reveal any aneurysms or structural defects to hint at the cause of the bleeding. She never had uncontrolled hypertension or severe coagulopathy during her ICU stay.

Seven patients required vasopressors; Table 2 gives details of the dosages. Two patients developed acute kidney injury requiring renal replacement therapy.

All patients were treated with antivirals, which included interferon 2-α and ribavirin. Oseltamivir was also used empirically, waiting influenza A, B, and H1N1 screening results. Broad spectrum antimicrobials were empirically added at the time of admission. Six patients developed secondary bacterial infections, with 2 patients developing positive respiratory bacterial cultures, 2 patients developed blood stream infection, and 2 patients had both respiratory and blood culture positivity. Respiratory pathogens included *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, and *Stenotrophomonas maltophilia*. Pathogens that grew in the blood stream included *A baumannii*, *Klebsiella pneumoniae*, *Enterobacter aerogenes*, and coagulase-negative staphylococcus. One patient had H1N1-positive coinfection.

Systemic steroids were used in all patients after it was observed that 1 patient had a dramatic improvement in oxygen requirements with initiation of steroids. Unfortunately, this effect was not consistently observed in the other patients.

At the time of writing this article, 5 of our patients had expired, 2 had recovered and were discharged home, and 1 patient remained intubated after developing intracranial hemorrhage, she has met death criteria but remains intubated as the patients family has not yet agreed to withdrawal of care. The median length of ICU admission was 11 days (range <1-56 days), while the median length of hospital admission was 9.5 days (range 1-54 days).

Both of the patients who survived were young (aged 26 and 28 years) health care workers. One of them (the janitor) had no comorbidities, while the other (the resident) was obese with a

body mass index of 37.8 and a history of glucose-6-phosphate dehydrogenase deficiency.

Discussion

We report on 8 patients with MERS-CoV who developed critical illness requiring admission to the ICU. All patients presented with acute respiratory symptoms necessitating intubation and mechanical ventilation in 7 patients. Previously, Arabi et al[4] reported on their experience in managing 12 confirmed or probable cases with MERS-CoV infection requiring ICU care. Their cases were from ICUs located in Riyadh and Al-Hasa, Saudi Arabia (located in the center and eastern part of the country, respectively). Geographically our ICU is located in the port city of Jeddah, which is in the western part of the Kingdom and close to the holy city of Mecca. The bulk of religious pilgrims use this regional hub for air and sea travel to reach Mecca. This might facilitate easier transmission of the virus to the city dwellers by the inbound and outbound travelers. Jeddah is also the country's main sea port for livestock imports, including camels, to the kingdom from the African horn countries.

Similar to Arabi et al's experience,[4] most of our patients were middle aged or elderly with comorbidities. However, it is troubling to note that we also had 2 very young patients who developed severe infection, one of whom needed ECMO. The finding of severe infection in young patients with relatively few comorbidities is novel, and physicians need to be aware that severe infection is not always confined to middle aged or elderly patients with comorbidities. The infected janitor was not an overweight person; however, the resident physician was morbidly obese. An interesting basic sciences research observation may explain the severity of MERS in obese patients.[5] The authors noted that Dipeptidyl peptidase 4 (DPP4) (an enzyme involved in glucose metabolism expressed on the surface of most cell types,[6,7]) is expressed in larger numbers in obese people compared to non-obese individuals. DPP4 has also been shown to be the port of entry of MERS-CoV into human cells.[5] It will be interesting to see if DPP4 levels influence the severity of the disease or present a modifiable risk factor for patients infected with MERS-CoV.

An unusual finding in our case series was the development of intracranial hemorrhage in a patient with no underlying structural disease. Although MERS-CoV has not been isolated from the brain of infected individuals, it is interesting to note that severe acute respiratory syndrome-associated coronavirus (SARS-CoV) has been isolated from the brain of patients.[8] Whether MER-CoV may be associated with the development of intracranial hemorrhage in our patient remains unclear.

Additionally, a significant proportion of our patients developed elevation in CK levels. Previous reports of SARS-CoV-infected patients had noted elevated CK levels in more than 30% of patients,[9] and a postmortem case series noted that focal myofiber necrosis was common and could possibly be immune mediated.[10] Therefore, it is possible that the elevated CK levels may be possibly related to myositis secondary to viral infection. We also reported the presence of lymphopenia in all the patients in our series. This finding has been well documented by other investigators as well.[4,11]

We noted universal failure of NIPPV in preventing need for intubation. This was also observed by Arabi et al[4] and Guery et al,[12] pointing to the futility of this form of therapy in critically ill patients with MERS-CoV infection. If Non-invasive positive pressure ventilation (NIPPV) is offered strict isolation, precautions (extended respiratory precautions) is advised due to the potential risk of significant aerosolization of respiratory droplets through the forced air coming out of the expiratory valve of the Bilevel positive airway pressure (BIPAP) mask. Physicians must have a low threshold to electively intubate the patient if there is extended failure of NIPPV.

Another important finding of our study was the high number of false-negative results we experienced when using nasopharyngeal swab specimens for MERS-CoV testing. Only 2 patients were confirmed by nasopharyngeal swab samples. This despite the fact that the samples were collected by nurses who had undergone training on proper collection methods by our infectious disease staff. Based on our experience, we now no longer rely on a negative nasopharyngeal sample in the presence of clinical findings to suggest MERS-CoV infection and attempt tracheal aspirates of bronchoalveolar lavages whenever possible.

During the course of their ICU stay, all of our patients developed ARDS and lung protective strategies with low tidal volume remained the mainstay of management. One patient required placement on ECMO. High frequency oscillation ventilation is not available in our ICU.

It is clear from our experience and that of others that these patients develop severe hypoxemia and need to be in a tertiary care facility where advanced therapeutic options are available.

All of our confirmed MERS-CoV cases were treated with oseltamivir, ribavirin, and interferon α 2B. Although good clinical data to support their use are currently not available, there are animal data that suggest improved outcomes in MERS-CoV-infected rhesus macaques treated with ribavirin and interferon α 2B.[13] Additionally Al-Tawfiq and colleagues[14] noted in an observational study that ribavirin and interferon α 2B may be effective in some patients, especially if started earlier in the course of the disease. In the absence of specific guidelines or proven therapies, we continue to use ribavirin and interferon α 2B in the treatment of all confirmed MERS-CoV cases.

The use of corticosteroids in the management of these patients remains another area of therapeutic uncertainty. Not only the dose to be used but also the duration of steroid therapy remains uncertain. A retrospective cohort[15] investigating the use of corticosteroids in SARS-CoV-infected patients reported a 20.7-fold increase in mortality and ICU admissions. Although we observed dramatic improvement in oxygen requirement in 2 patients after initiation of corticosteroids, this effect was not observed in other patients. The specific role of corticosteroids in MERS-CoV infection remains unknown and their use remains at the discretion of the treating physician on a case-by-case basis.

The major limitation of our study is the small sample size. As such more collaborative research is needed to get a better

understanding on how MERS-CoV-infected patients who develop critical illness present and what their optimal management should be.

In conclusion, MERS-CoV-infected patients who develop critical illness often present with respiratory symptoms requiring mechanical ventilation. They usually have lymphopenia and a significant proportion have CK elevation. Management remains largely conservative as there are currently no proven specific therapies. They should ideally be managed in a tertiary care facility where refractory hypoxemia can be treated with salvage therapies.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

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