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Intensive Care Management of Middle East Respiratory Syndrome

An Essay
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in General Intensive Care Medicine

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Abstract

Background: Middle East respiratory syndrome (MERS) is a respiratory disease caused by a newly recognized coronavirus (MERS-CoV). It was first reported in 2012 in Saudi Arabia and is thus far linked to countries in or near the Arabian Peninsula (United Arab Emirates [UAE], Qatar, Oman, Jordan, Kuwait, Yemen, and Lebanon). As of May 2014, two cases had been reported in the United States, both in men who had recently returned from Saudi Arabia.

Aim of the Work: The aim of the essay is to through light on the Middle east respiratory syndrome corona virus infection concerning it's pathophysiology, diagnosis, prevention and ICU management.

Methodology: Middle East respiratory syndrome (MERS), also known as camel flu, is a viral respiratory infection caused by the MERS-coronavirus (MERS-CoV). Symptoms include fever, cough, diarrhea, and shortness of breath. As of June 20, 2015, 1,334 laboratory-confirmed cases of infection with MERS-CoV have been reported to the World Health Organization (WHO), including at least 471 related deaths. Coronaviruses are the largest of all RNA viruses, with positive single-stranded RNA genomes of 26-32 kb. The virus appears to have originated in bats. Transmission through contacts with animal e.g camel ,spread of MERS-CoV from person to person has been evidence of limited Spread.

Conclusion: Antiviral treatment can be actively considered since their efficacy has been confirmed in laboratory studies and they have shown some degree of efficacy in retrospective clinical studies.

Mycophenolic acid, chloroquine, chlorpromazine, and loperamide have a demonstrated antiviral effect against MERS-CoV in laboratory tests.

Keywords: Intensive Care Management, Middle East, Respiratory Syndrome, pathophysiology, diagnosis

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ARDS	acute respiratory distress syndrome
ALI	air-liquid interface
ACE2	angiotensin converting enzyme 2
BAL	bronchoalveolar lavage
BOOP	bronchiolitis obliterans organizing pneumonia
CDC	Centers for Disease Control and Prevention
CPE	cytopathic effects
CXCL	CXC-motif chemokines ligand
CrCl	creatinine clearance
Ct	cycle threshold
DPP4	dipeptyl peptidase 4
DIC	disseminated intravascular coagulation
DAD	diffuse alveolar damage.
EMC	Erasmus Medical Center
HAE	human airway bronchial epithelium
HPA	Health Protection Agency
IFN	interferon
IP-10	inducible protein-10
IRF	interferon regulatory factors

ISARIC	International Severe Acute Respiratory and Emerging Infection Consortium
IMV	invasive mechanical ventilation
ILI	influenza-like illness
IPC	infection prevention and control
IFA	assaysimmunofluorescence
IHR	International Health Regulations
MERS	Middle East respiratory syndrome
MDMs	monocyte-derived macrophages
MCP-1	Monocyte chemotactic protein-1
MDA5	melanoma differentiation-associated protein 5
PPE	personal protective equipment
RdRp	RNA-dependent RNA polymerase
RIVM	National Institute of Public Health and Environment
RIG	retinoic inducible-acid gene
RT-PCR	real-time polymerase chain reaction
RdRp	RNA-dependent RNA polymerase
RBSD	receptor binding subdomain
SENIC	Study on the Efficacy of Nosocomial Infection Control
SARS-Cov	severe acute respiratory syndrome coronavirus
WHO	World Health Organization

Introduction

Middle East respiratory syndrome (MERS) is a respiratory disease caused by a newly recognized coronavirus (MERS-CoV). It was first reported in 2012 in Saudi Arabia and is thus far linked to countries in or near the Arabian Peninsula (United Arab Emirates [UAE], Qatar, Oman, Jordan, Kuwait, Yemen, and Lebanon). As of May 2014, two cases had been reported in the United States, both in men who had recently returned from Saudi Arabia **(Rha et al., 2015).**

One of the most important cells of the innate immune system is the macrophages; their function is to eliminate pathogens, to present antigens to T cells, and to produce cytokines and chemokines to maintain homeostasis and modulate the immune response in tissues. Compared with severe acute respiratory syndrome coronavirus (SARS-Cov), MERS can establish a productive infection in monocyte-derived macrophages (MDMs) and macrophages. This then induces a release of proinflammatory cytokines, leading to severe inflammation and tissue damage, which may manifest clinically as severe pneumonia and respiratory failure. Vascular endothelial cells located in the pulmonary interstitium may also be infected by MERS-CoV, and, because MERS-CoV receptor

DPP4 is expressed in different human cells and tissues, dissemination of the infection may occur. This may explain the increased severity and higher fatality rate compared with the SARS-CoV infection. **(Zhou et al., 2014)**.

Physical examination associated with MERS-CoV infection is similar to those presenting with any flulike illness, including the following: Fever, Rhinorrhea, mostly clear, Pulmonary findings such as rhonchi and rales (some patients may have a normal auscultation) and Tachycardia, mostly secondary to fever. Evidence shows that lower respiratory tract specimens such as bronchoalveolar lavage (BAL), sputum, and tracheal aspirates contain the highest viral loads. Some cases, including the second US case, have been confirmed only in sputum after negative or equivocal results on PCR for MERS-CoV in nasopharyngeal and oropharyngeal specimens. The recommended algorithm for detection of MERS-CoV includes testing using rRT-PCR. There are two target sites on the novel coronavirus genome identified that can be sequenced; these are located in the RNA-dependent RNA polymerase (RdRp) and N genes (**Corman et al., 2012).**

To consider a case as laboratory confirmed, one of the following criteria must be met: (1) a positive PCR result for at least 2 different specific targets on the MERS-CoV

genome or (2) one positive PCR result for a specific target on the MERS-CoV genome and an additional different PCR product sequenced confirming known sequences of MERS-CoV

A case with a positive PCR result for only one specific target in a patient with a history of possible exposure and compatible clinical presentation is considered probable. Serologic testing is available for the evaluation of MERS-CoV infection or exposure. The serum specimens should be collected during the acute stage of the disease and repeated during the convalescence **(Available at http://www.who.int/csr/disease/coronavirus_infections/en/)**

The World Health Organization (WHO) and the United States Centers for Disease Control and Prevention (CDC) have issued recommendations for the prevention and control of Middle East respiratory syndrome coronavirus (MERS-CoV) infections in healthcare settings. An increased level of infection control precautions is recommended when caring for patients with probable or confirmed MERS-CoV infection compared with that used for patients with community-acquired coronaviruses or other community-acquired respiratory viruses. The WHO recommends that standard and droplet precautions be used

when caring for patients with acute respiratory tract infections **(World Health Organization. Middle East respiratory syndrome coronavirus (MERS-CoV) summary and literature update – as of May 2014).**

Rapid development of effective therapeutic options is a high priority since no antivirals are approved for the treatment of coronavirus infection nor vaccines available for prevention. Management of Middle East respiratory syndrome (MERS) coronavirus (MERS-CoV) infection is supportive; this includes hydration, antipyretic, analgesics, respiratory support, and antibiotics if needed for bacterial superinfection. Experience during the SARS outbreak showed inconsistent results when antiviral therapy was used. One randomized trial compared ribavirin versus interferon1 alpha in SARS and showed no advantage of ribavirin over interferon. A recent study demonstrated activity of mycophenolic acid against the novel MERS-CoV; its potent in vitro activity may allow it to be used as monotherapy. Ribavirin and interferon alfa have synergistic actions in vitro effects against the virus, but their role (if any) in the treatment of MERS remains unknown **(Zhao, 2003).**

One small observational study of 5 patients with MERS-CoV infection receiving ribavirin in combination with

interferon alfa 2b in Saudi Arabia failed to show any benefit. These patients were all critically ill and on mechanical ventilation, and the median time from admission to therapy was 19 days, perhaps too late to demonstrate any benefit **(Zhao, 2003).**