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Recognizing and Managing Emerging Infectious Diseases in the Emergency Department

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Abstract

With population shifts, increased travel, and climate change, the spread of emerging and re-emerging infections is increasing. Although encountering a patient with an emerging infection on any given emergency department shift is unlikely, missing a diagnosis could have profound consequences for the patient, healthcare workers, and the patient's close contacts. This review provides a framework to evaluate, diagnose, and treat a returning traveler with suspected Middle East respiratory syndrome, chikungunya virus, or Zika virus—3 recently emerged infections. All may present with nonspecific viral-like symptoms and are easily missed if an appropriate travel history is not obtained. A high level of vigilance and proper disposition will enable the emergency clinician to effectively diagnose, manage, and contain these diseases.

Case Presentations

A 60-year-old man presents to the ED complaining of a fever. The triage note reports that the patient has had 2 days of cough, fever, and mild diarrhea, and he feels short of breath. His temperature is 39.1°C (102.4°F); blood pressure, 138/72 mm Hg; pulse, 104 beats/min; respiratory rate, 18 breaths/min; and oxygen saturation, 98% on room air. On physical examination, you hear scattered rhonchi in both of the patient's lungs. On further questioning, he tells you that he was in Saudi Arabia for a business trip last week. You remember hearing about an illness in that region that causes fever, and you wonder what you should do next...

A 42-year-old nursing colleague of yours presents to the ED with fever, headaches, and severe joint pain. She has a history of diabetes, hypertension, and early arthritis. She frequently visits the Dominican Republic for work and returned 5 days ago from a trip there. She is convinced that she has dengue fever because she had heard there was an outbreak of this disease while she was there. On physical examination, she looks uncomfortable. She has pain and swelling over her fingers, wrists, and ankles. You consider whether isolation and testing are called for...

A 27-year-old woman presents to the ED with a fever, a rash, headache, and some conjunctival irritation. You are relieved to find that she is comfortable-appearing and has no meningismus. Her vital signs are reassuring: blood pressure, 117/78 mm Hg; pulse 90 beats/min; respiratory rate, 16 breaths/min; oxygen saturation, 99% on room air; and temperature, 38°C (100.5°F). She states that she just got back from her honeymoon in Puerto Rico. You seem to remember something about an outbreak of something in Puerto Rico, but cannot recall the details. You prescribe acetaminophen for the headache and fever and order laboratory tests and a urine pregnancy test, but you wonder if there is something else that you should be checking...

Introduction

Emerging infections are broadly defined as diseases "…whose incidence in humans has increased in the past 2 decades or threatens to increase in the future."[1] They usually cross national boundaries and are determined by complex interactions between the environment and human and animal ecosystems.[2] *Re-emerging infections* are diseases once considered to be major global health problems that had fallen to such low levels that they were no longer considered public health threats, but are now showing upward trends in incidence or prevalence worldwide. Malaria, tuberculosis, Zika infection, and chikungunya are examples of re-emerging infections.

Occurring less frequently, an emerging infection can also be defined as a newly identified and previously unknown infectious agent that causes public health problems either locally or internationally. These new diseases often result from changes in the environment and the interaction between humans and disease vectors. Less frequently, an emerging disease can be a previously unrecognized infection in the process of undergoing ecological transformation.[3] Ebola and Lassa fever are classic examples of this. In this article, Middle East respiratory syndrome (MERS) can be classified as an emerging infectious disease. Factors such as urbanization, deforestation, ease of global travel, climate change, and weak healthcare systems are contributing factors associated with the occurrence of both categories of diseases.[4,5]

MERS, chikungunya virus (CHIKV) infection, and Zika virus (ZIKV) infection have had recent emergence and re-emergence worldwide. Globalization, rapid urbanization, and ease of travel bring patients with emerging or re-emerging infections to emergency departments (EDs) all over the world. While these diseases infrequently cause primary infection in the United States, the emergency clinician must recognize the ill traveler and alert public health authorities when appropriate. This vigilance requires active awareness of the current outbreaks on a global scale and risk factors for illness. This issue of *Emergency Medicine Practice* reviews 3 diseases—MERS, CHIKV infection, and ZIKV infection—that remain active and pose a public health threat.

Critical Appraisal of the Literature

A search was performed in PubMed for literature published between 2012 and 2017. For MERS, the search term *Middle East respiratory syndrome* yielded 10,009 articles; *Middle East respiratory syndrome coronavirus* yielded 1074 articles in English, and *Middle East respiratory syndrome* AND *emergency* yielded 324 articles in English. Articles included review articles, commentaries, case-control and cohort studies, and observational studies. No randomized controlled trials exist for the treatment of this disease. Ultimately, 104 articles were identified for close review. Reviews of the World Health Organization (WHO), the United States Centers for Disease Control and Prevention (CDC) and the Saudi Arabian Ministry of Health websites were also performed.

For CHIKV, the search term *chikungunya* yielded over 3400 articles in English; using *chikungunya alphavirus* yielded over 2000 results; and *chikungunya alphavirus* AND *travel* yielded 194 articles. Most articles were reviews, expert opinions, case reports, and observational studies of pharmacologics, viral microbiology, and characterization of outbreaks occurring largely in Africa, South and Southeast Asia, the Caribbean, and Central and South America. There is a paucity of vigorous studies for this disease. There were only 4 randomized controlled trials related to vaccines and treatment. A total of

82 articles were included for final review. A seminal study on the disease describing clinical progression and treatments was conducted during a large outbreak on La Reunion Island in the Indian Ocean. Updated guidelines and reports from the WHO and the CDC also were also reviewed.

For ZIKV, a literature search with the single term *Zika* yielded 2082 articles in the English language. Searching *Zika* AND *travel* yielded 267 articles, and the terms *Zika* AND *emergency* yielded 220 articles. There were no randomized controlled trials, and the articles focused primarily on reviews and case reports, evaluation studies, epidemiological reports, and summaries of biochemical research and pharmacologic interventions. A total of 38 articles were included for final review, and WHO and CDC updates and guidelines were also examined.

Etiology and Pathophysiology

Table 1 summarizes the signs and symptoms, incubation period, testing, and complications for MERS, CHIKV infection, and ZIKV infection.

Etiology and Pathophysiology of MERS

MERS is a single-stranded RNA coronavirus first identified in Saudi Arabia in 2012.[6] The index case involved a 68-year-old man who presented with a respiratory illness and no identifiable organism (using testing technology available at that time). Further investigation identified a novel coronavirus (now called *Middle East respiratory coronavirus* [MERS or MERS-CoV]) as the etiology of this illness, and, subsequently, the causative agent of cases in 26 other countries throughout the world.[7-9] Since the first cluster of cases in 2012, the only other large outbreak occurred in South Korea in 2015, during which 186 people were infected.[10,11] Other identified human coronaviruses are already-known infectious organisms most commonly responsible for causing respiratory or enteric infections.

The MERS coronavirus spreads through zoonotic transmission, with the Arabian camel as the likely animal reservoir. Bats were initially believed to be the source of infection because they are a reservoir for other coronaviruses, but they were ultimately ruled out as the source. Transmission to humans from camels likely occurs through contact with camel saliva, milk, or meat.[12-14] Once infected, human-to-human transmission may occur through droplets, airborne transmission, or fomites. Unlike other coronaviruses that are rapidly and relatively easily transmitted (such as severe acute respiratory syndrome [SARS]), MERS is slightly harder to transmit and has resulted in an overall lower number of cases in both local and international outbreaks. Human-to-human contact is suspected for many cases of new infections, particularly among healthcare workers. In a case series of 190 persons, 74% had no known contact with an animal source.[12]

The incubation period before symptom onset lasts between 5 and 12 days.[14,15] Once symptomatic, patients develop an influenza-like illness, with fever and cough as the predominant symptoms, often in conjunction with diarrhea and shortness of breath. **(See Table 1.)** The median age of infected

Table 1. Signs and Symptoms, Incubation Period, Tests, and Complications of Middle East Respiratory Syndrome, Chikungunya Virus Infection, and Zika Virus Infection

Disease	Signs and Symptoms	Incubation Period	Tests	Complications
Middle East respiratory syndrome	• Fever • Cough • Shortness of breath • Diarrhea • Vomiting	• 5 to 12 days	• Real-time reverse transcription polymerase chain reaction • ELISA • Immunofluorescence assay	• Pneumonia with respiratory failure • Acute respiratory distress syndrome • Multiorgan system failure
Chikungunya virus infection	• Fever • Symmetric distal arthralgias • Joint swelling • Vomiting/diarrhea • Maculopapular rash • Headache • Extreme fatigue/asthenia	• 3 to 7 days	• Lymphopenia (nonspecific) • Real-time reverse-transcription polymerase chain reaction • ELISA • Immunofluorescence assay	• Arthritis • Chronic arthralgia • Guillain-Barré syndrome • Cranial nerve palsies • Meningoencephalitis • Myocarditis • Hepatitis • Multiorgan failure
Zika virus infection	• Fever • Rash • Headache • Conjunctivitis • Arthralgias • Myalgias	• 2 to 7 days	• ZIKV nucleic acid testing • ZIKV immunoglobulin M serology • Plaque reductions • Neutralization test	• Congenital Zika syndrome • Guillain-Barré syndrome • Meningoencephalitis • Thrombocytopenia and risk of hemorrhage

Abbreviations: ELISA, enzyme-linked immunosorbent assay; ZIKV, Zika virus.

patients is 50 years, with few cases in persons younger than 26 years, and even fewer infections in children.[16,17] MERS is slightly more prevalent in men, who account for 64% of cases.[16] The clinical disease is often mild, but can be a severe illness with multiorgan dysfunction. As of November 2017, 2121 cases have occurred worldwide, with 630 deaths (35.6%). New infections are still occurring in the Middle East.[9,14,18]

An outbreak occurred outside of the Middle East in 2015, when a traveler returning to South Korea from Saudi Arabia caused multiple transmissions because of delayed identification of the illness and failure to isolate him at the healthcare facilities where he originally presented. This patient was responsible for infecting 28 other individuals. In a single hospital, 82 patients were infected by another infected person.[11,19] Almost all cases in the South Korean outbreak occurred through hospital transmission, which raises the importance of obtaining a history of sick contacts during outbreaks and not relying solely on travel history for disease suspicion. Over a period of 2 months, just under 200 patients were infected through this outbreak, although the 20% death rate in South Korea was lower than has been reported from Middle Eastern outbreaks.[20] As in South Korea, other outbreaks have demonstrated that up to one-third of new infections were nosocomial, confirming that healthcare workers are at significant risk from contact with infected patients.[16] In a case-control study of 292 healthcare workers, the most commonly infected workers were radiology technicians, followed by nurses, suggesting that close contact is necessary for transmission.[21]

Etiology and Pathophysiology of CHIKV

CHIKV is an RNA virus belonging to the *Alphavirus* genus of the Togaviridae family. It is an arbovirus transmitted to humans after a bite of an infected *Aedes aegypti* or *Aedes albopictus* mosquito. Rare causes of transmission include vertical transmission from mother to fetus, which has been associated with subsequent long-term neurocognitive delays in infected children.[22] There have been no documented cases of transmission via breast milk.[23] Transmission through infected blood products and organ donation is plausible when viremia is high, prior to the onset of symptoms.[24,25]

CHIKV infection outbreaks in urban areas have followed spillover infections from African enzootic transmission cycles.[26] The first known outbreak was characterized in Tanzania in 1953, and since then, periodic outbreaks have occurred in other parts of Africa and Asia. In 2004, a large outbreak began in Kenya, which spread to India and the islands in the Indian Ocean. Afterward, transmission was documented in northern Italy, France, and many countries in South and Southeast Asia when infected travelers returned to their home countries.[27,28] The largest documented outbreak occurred on the island of La Reunion, in the Indian Ocean, where an estimated 35% of the island's population became infected.[29] The virus did not reach the Americas until December 2013, on the island of Saint Martin.[30] It subsequently spread to the rest of the Caribbean, Central America, and South America.[31] Since 2014, there have been 4059 travel-related cases of CHIKV infection in 49 states of the United States (excepting Wyoming), according to the CDC. In addition, local transmission has been reported widely in United States territories, with over 5000 cases reported. The majority of the cases have been found in Puerto Rico, but also in the United States Virgin Islands and American Samoa. Florida has had 12 locally transmitted cases, and most recently, there was 1 reported case in Texas in 2015.[32]

Infection with CHIKV is rarely fatal, but it has a severe acute phase and often causes subsequent chronic arthralgia. Up to 50% of patients develop chronic joint symptoms that are relapsing and remitting, lasting months to years.[33] The vast majority of infected patients are symptomatic, and fewer than 15% who are asymptomatic show evidence of antibody seroconversion.[26] Following an incubation period of 3 to 7 days, a high-grade fever (> 38.9°C [102°F]) appears abruptly, lasting up to 10 days. The defining feature is arthralgia, which is usually bilateral, symmetric, and involves distal joints (wrists, fingers, ankles) more than proximal joints (knees, hips, shoulders).[34] The pain is often intense and disabling, hence the name "chikungunya," which comes from the Makonde language, and means "that which bends up."[35] A rash occurs 20% to 80% of the time and can be vesicular, bullous, or maculopapular.[26,36] Other symptoms include headache, myalgia, gastrointestinal symptoms, joint swelling, and severe fatigue or asthenia. **(See Table 1, page 3.)** Severe and rare sequelae also have been described in the setting of outbreaks, including Guillain-Barré syndrome, cranial nerve palsies, meningoencephalitides, myocarditis, hepatitis, and multiorgan failure.[37,38] Older patients with cardiovascular disease, diabetes, and respiratory conditions tend to have more-severe presentations and often require hospitalization.[26,39]

Etiology and Pathophysiology of ZIKV

ZIKV is an RNA virus from the *Flavivirus* genus in the Flaviviridae family. It is closely related to the dengue virus, the yellow fever virus, the West Nile virus, and the Japanese encephalitis virus.[40-42] A sentinel case was reported in 1947 in a Rhesus monkey in the Zika forest outside of Entebbe, Uganda. The virus was soon isolated and traced to the transmitting vector, the *Aedes* mosquito.[40,42,43] The first human infections were reported in Africa in the 1950s. The first large outbreak occurred in 2007

in the Yap Islands of Micronesia, in which over 70% of the population became infected. This was followed by outbreaks in French Polynesia and other South Pacific islands in 2013.[44] It is theorized that these outbreaks provided the strain for the Brazilian outbreak of 2015, possibly introduced during the FIFA World Cup in 2014 or during the Va'a World Championships canoe race held in Rio de Janeiro in August 2014.[41-43] On February 1, 2016, ZIKV infection was declared a public health emergency of international concern by the WHO, mostly due to an association between ZIKV infection and congenital microcephaly. As of November 18, 2016, the WHO no longer considered ZIKV infection to be a public health emergency of international concern.

Transmission of ZIKV is mostly through the *Aedes* mosquito vector; however, other possible forms of transmission include blood transfusion, sexual intercourse, and vertical transmission from mother to fetus.[42,45] The incubation period is believed to be between 2 and 7 days, although only 1 in 5 patients manifest clinical symptoms. The infection presents as a mild viral syndrome, with 3 to 7 days of self-resolving fever, maculopapular rash, conjunctival irritation or congestion, and arthralgias that may last longer than other symptoms.[44] **(See Table 1, page 3.)**

ZIKV infection became a global concern because of its association with congenital microcephaly. Viral particles have been found in amniotic fluid, fetal brain tissue, and in the cerebrospinal fluid of fetuses. ZIKV is unique among Flaviviridae for its neurotropism and its ability to cross placental and fetal blood-brain barriers. In addition to the association with congenital microcephaly, ZIKV infection is also associated with increased incidence of Guillain-Barré syndrome, meningoencephalitis, and various congenital orbital syndromes.[46-49] The mechanism for the microcephaly and the infectious process in general is still under investigation, but it is known to cause dysregulation in cellular metabolism and increase apoptotic pathways within the cell.[46,49-52]

Differential Diagnosis

In general, the formation of a comprehensive differential diagnosis underscores the importance of obtaining a detailed travel history. **(See Table 2.)** To help elucidate the diagnosis, inquire about use of malaria prophylaxis and vaccination history as well as the patient's activities while abroad, including visits to rural locations, exposures to animals and animal products, bites, sexual encounters, and eating and drinking practices. In most cases, the differential diagnosis should include more common causes of fever.

Differential Diagnosis of MERS

For the patient at risk for MERS based on travel history to the Arabian Peninsula or contact with a person infected with MERS in the prior 2 weeks, the differential includes most organisms or disease processes that cause respiratory illnesses. One must consider the other infectious coronaviruses that cause respiratory illness (most commonly, the 3 strains of human coronaviruses). SARS was a concern in travelers from Asia during its outbreak, but there have been no cases since 2004, and therefore it does not currently enter into the differential.[53] Traditional respiratory pathogens are common and warrant consideration (eg, adenovirus, human metapneumovirus, respiratory syncytial virus, rhinovirus). In addition, bacterial causes of pneumonia (*Streptococcus pneumoniae, Mycoplasma, Staphylococcus aureus*) must be considered as potential pathogens. If symptoms occur during the applicable time of year for a given locale, influenza virus could also result in symptoms similar to MERS.

Differential Diagnosis of CHIKV Infection

In the acute phase of CHIKV illness, the 2 most important diseases to consider in travelers from endemic areas are malaria and dengue. Malaria infection with *Plasmodium falciparum* can cause severe illness in travelers, especially in children. Dengue infection presents similarly to CHIKV infection and, rarely, can progress to hemorrhagic complications. Depending on where the patient traveled and their

Table 2. Travel Risk Exposures and Associated Infections

Risk Exposure	Associated Infections
Unprotected sex	Acute HIV infection, hepatitis B, hepatitis C, syphilis
Drinking/eating contaminated water or food	Amebiasis, typhoid and paratyphoid fever*, hepatitis A, hepatitis E
Exposure to lakes and slow-moving rivers	Schistosomiasis
Tick bites	Spotted fever rickettsiosis*, relapsing fever, Crimean-Congo hemorrhagic fever
Exposure to animals	Leptospirosis, MERS, rabies, Q fever, *Echinococcus* (tapeworm)
In-country hospitalization/ medical tourism	Multidrug-resistant bacteria, hepatitis B
Cave exploration	Histoplasmosis, coccidioidomycosis
Mosquito bites	Malaria*, dengue*, chikungunya, Zika, yellow fever
Exposure to flies	African sleeping sickness, leishmaniasis, onchocerciasis

*Most common in returning travelers.
Abbreviations: HIV, human immunodeficiency virus; MERS, Middle East respiratory syndrome. © www.ebmedicine.net

adherence to chemoprophylaxis for malaria, CHIKV infection, dengue, or malaria might be more likely. Reviewing the CDC's Travelers' Health website (wwwnc.cdc.gov/travel) can be useful to assess this risk. **See Table 3** for other useful travel websites. In heavily endemic areas, co-infection is possible with dengue and ZIKV.[54,55] Meningococcal infection must be considered in ill-appearing travelers presenting with fever, viral syndrome, and/or rash. Viral hemorrhagic fevers, such as Ebola, Lassa, and Marburg, should also be considered in the context of worldwide outbreaks. More common causes to be contemplated are acute HIV infection, Group A *Streptococcus*, influenza, and infectious mononucleosis.

Other diseases presenting with fever, rash, and arthralgia are measles, rubella, parvovirus B19, ZIKV, and other alphaviruses such as Ross River virus and Barmah Forest virus in patients who recently traveled to Australia.[56] Exposure to animal urine, tick bites, or contaminated food or water broadens the infection possibilities to leptospirosis, African tick-bite fever, relapsing fever and typhoid/paratyphoid fever, respectively. Patients presenting in the chronic stage of the disease might have signs and symptoms resembling seronegative rheumatoid arthritis or other causes of inflammatory joint disease.[57]

Differential Diagnosis of ZIKV Infection

With ZIKV infection, the differential is made difficult by its nonspecific and often mild presentation. Any viral syndrome besides ZIKV infection also should be considered, but particularly the arboviruses mentioned previously (eg, dengue, yellow fever, West Nile) should be given stronger consideration as possibilities in the returning traveler. If congenital abnormalities have been discovered, the TORCH infections (toxoplasmosis, other [syphilis, varicella-zoster, parvovirus B19], rubella, *Cytomegalovirus*, and herpesviruses) are also considerations.

Prehospital Care

Prehospital Care for MERS

For MERS or other respiratory illnesses, the most important component of prehospital care is obtaining the travel history. If patients with respiratory illness and fever report recent travel to a region of the Middle East where MERS is active (Saudi Arabia, most commonly), prehospital personnel should place a mask on the patient and notify the receiving ED of the possibility of a traveler from a MERS-endemic region with fever. Prehospital providers should follow all other applicable protocols for the management of patients with respiratory illnesses, including providing supplemental oxygen or performing airway interventions as necessary.

Prehospital Care for CHIKV Infection

For CHIKV infection, no specific precautions are required in the prehospital setting. Prehospital personnel should practice universal precautions and isolate the patient until other travel-related transmissible illnesses are ruled out. Supportive measures, including pain control, might be required en route due to the painful presentation of the disease.

Prehospital Care for ZIKV Infection

For ZIKV infection, no specific precautions are necessary other than routine personal protective equipment, though given that the diagnosis is likely unknown at this point, a mask may be prudent. If necessary, the patient may be given supportive care such as oxygen if hypoxic, or intravenous crystalloid fluids for signs of dehydration.

Emergency Department Evaluation

Triage

Emergency clinicians first evaluating the patient (ideally, the triage nurse) must implement isolation protocols for the patient with known or suspected MERS. One goal in the evaluation and treatment of a patient with MERS is prevention of secondary transmission to other patients in the ED as well as

Table 3. Traveler Health Websites

Originating Organization	Website Address
United States Centers for Disease Control and Prevention	https://wwwnc.cdc.gov/travel
World Health Organization, International Travel and Health	http://www.who.int/ith/en/
International Society of Travel Medicine	http://myistm.istm.org/istm/home
United Kingdom National Travel Network and Center	https://travelhealthpro.org.uk/
World Health Organization Disease Outbreak News	http://www.who.int/csr/don/en/
Pan American Health Organization/World Health Organization, Health Emergencies affecting the Americas	http://www.paho.org/disasters/index.php?lang=en
Public Health Agency of Canada	https://www.canada.ca/en/public-health/services/travel-health.html

healthcare workers. Patients should wear a mask and staff should place them in a private room under droplet precautions. Any staff member within 1 meter of the patient should wear a mask. Emergency clinicians and all hospital staff must follow strict handwashing protocols, given the risk of nosocomial spread of infection. In an analysis of the South Korean outbreak, the MERS virus was isolated in the air, in corridors, in patient rooms, and on multiple surfaces.[58] In a prospective analysis of 101 cases acquired in a Riyadh hospital, more than half of the infections occurred in the ED, which had 150 beds and evaluated 250,000 patients annually.[59]

History

A thorough travel history is paramount for a reasonable estimation of the risk for major infections affecting travelers. The history should include specific countries and areas visited (rural or urban), insect bites, contact with sick animals or humans, chemoprophylaxis, and vaccination status. Other important historical information includes the timing of the onset of symptoms relative to travel or contacts, current medications, and recent hospitalizations either in the United States or abroad. A complete review of symptoms will help point toward a specific diagnosis. MERS often begins with an influenza-like illness, including fever, cough, myalgias, arthralgias, and sore throat. Approximately one-third of patients report vomiting and diarrhea. The defining features of CHIKV are fever with joint pains. Other nonspecific viral-like symptoms may also be present, making it difficult to differentiate from malaria or dengue. Patients with ZIKV usually complain of fever, commonly in association with conjunctivitis, headache, and arthralgias.

Physical Examination

Fever and tachycardia are the most common findings on physical examination for the diseases discussed in this issue. A complete physical examination should be performed that includes a head/eye/ear/nose/throat examination, a careful skin examination, cardiopulmonary examination, and abdominal examination. MERS does not have characteristic physical examination findings. Patients with CHIKV infection often present with symmetric swelling of the joints. Skin manifestations, when present, occur primarily on the face, trunk, and extremities. Patients with ZIKV infection commonly have bilateral conjunctivitis without any purulent discharge. The characteristic rash of ZIKV infection is a fine, often pruritic maculopapular rash spread diffusely over the body, including the palms of the hands and soles of the feet, without any characteristic distribution.[60] **(See Figures 1 and 2.)**

Figure 1. Zika Virus Rash on Arm

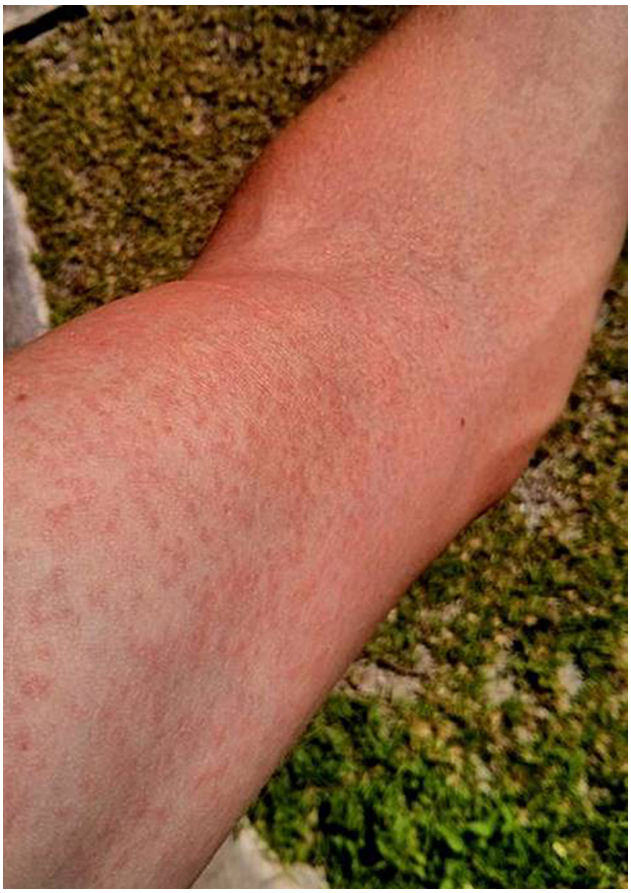

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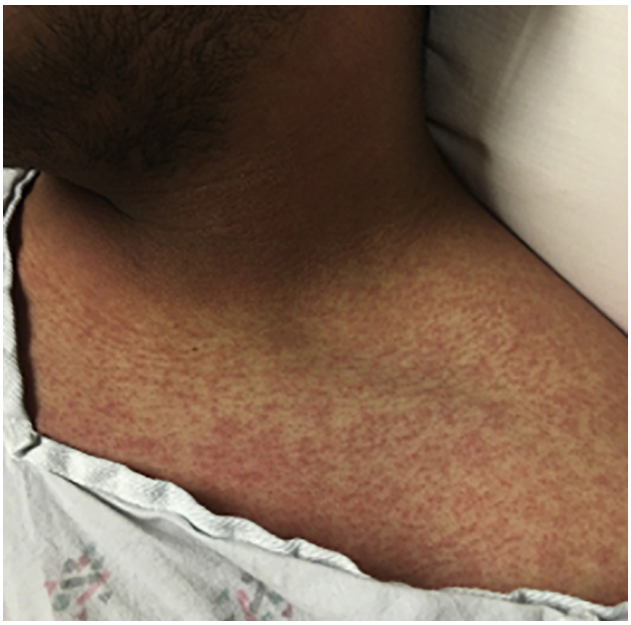
Figure 2. Zika Virus Rash on Chest



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Diagnostic Studies

Diagnostic Studies for MERS

To make the diagnosis of MERS, specialized testing is required. To access this test, the patient must have the appropriate exposure history (either travel to an endemic area or close contact with an infected person). The Ministry of Health in Saudi Arabia, WHO, and CDC recommend testing patients who present with symptoms within 14 days of potential exposures. In the appropriate clinical setting, polymerase chain reaction (PCR) testing of nasal secretions or tracheal aspirates of intubated patients should identify the virus.[61] Bronchial secretions are preferred when the patient is intubated or undergoing bronchoscopy. Serologic testing is also available using enzyme-linked immunosorbent assay (ELISA), immunofluorescence assay (IFA), or protein microassay.[14] These tests are not typically available at most healthcare centers, and should be obtained in consultation with infectious disease specialists or department of health personnel, depending on hospital protocol. Given the inability for hospitals to obtain onsite rapid testing results, it is imperative for institutions to have clear isolation protocols for patients who are at risk and are being ruled out for MERS.

No specific laboratory testing is indicated for patients with suspected MERS, other than those needed to assess for other causes of fever and respiratory illnesses. In one study, compared with other patients with influenza-like respiratory illnesses, those with MERS infection had lower white blood cell (WBC) counts, lower neutrophil counts, and slightly higher transaminases, although these tests cannot effectively distinguish MERS from other influenza-like illnesses.[62] A chest radiograph is recommended for the identification of pneumonia or for acute respiratory distress syndrome in severely ill patients. Given the prevalence of pulmonary symptoms, imaging is indicated. A regular radiograph will likely demonstrate interstitial changes, particularly in the periphery, early in the course of disease if abnormalities are present. **(See Figure 3.)** Chest computed tomographic (CT) findings are more likely to be ground-glass changes rather than consolidation.[63]

Diagnostic Studies for CHIKV Infection

Laboratory abnormalities are nonspecific for CHIKV disease. These include elevated liver enzymes, lymphopenia, hypocalcemia, and, rarely, thrombocytopenia.[64,65] In the rare patient with symptoms of meningoencephalitis, lumbar puncture results will often be typical for a viral infection, with normal glucose, elevated protein, and increased WBC count with a lymphocyte predominance. CHIKV RNA might not be detected in cerebrospinal fluid.

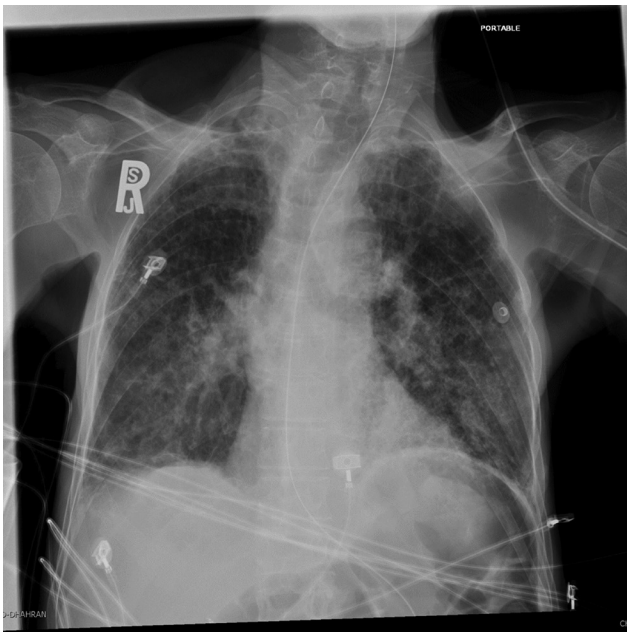
Laboratory tests specific for detecting CHIKV are commercially available but are not readily available in most hospitals. These tests include reverse transcription PCR (RT-PCR) to detect viral RNA, and ELISA/IFA tests for antibodies. Antibody testing has shown cross-reactivity with other alphaviruses, but is much simpler to perform and less expensive. In general, RT-PCR is the most sensitive and diagnostic. It is reasonable to treat patients empirically, but suspected cases should be reported to local public health officials to help facilitate appropriate testing and monitoring either in the ED or in the outpatient setting. The CDC, California and New York state health departments, and a single commercial laboratory (Focus Diagnostics) offer testing for CHIKV.

Diagnostic Studies for ZIKV Infection

A pregnancy test is always indicated in women of childbearing age, but it is particularly necessary when ZIKV infection is considered. The diagnosis of ZIKV can, potentially, be made using clinical criteria alone for patients who traveled to an endemic area within the last 1 to 2 weeks who have a maculopapular rash and the characteristic syndrome of a low-grade fever, frontal or retro-orbital headache, nonpurulent conjunctivitis, and arthralgias.

If confirmation of diagnosis is necessary, the test of choice is real-time RT-PCR of serum (most common), urine, or other bodily fluids (eg, cerebrospinal fluid in patients with neurologic complaints

Figure 3. Chest X-Ray Showing Interstitial Infiltrate in a Patient With Middle East Respiratory Syndrome



Jaffar A. Al-Tawfiq, Kareen Henedi. Middle East respiratory syndrome coronavirus: a case-control study of hospitalized patients. *Clinical Infectious Diseases.* 2014. Volume 59, Issue 2, pages 160-165. © Infectious Diseases Society of America and Oxford University Press. Used with permission.

or findings), though it may not be available at all facilities and may need to be sent to the CDC or other regional laboratory. This test becomes positive about 5 to 7 days after initial infection or 2 to 5 days after symptoms develop. Immunoglobulin M (IgM) serum antibodies may also be used to obtain a diagnosis; however, cross-reactivity with other flaviviruses (especially dengue) is very common, so using antibodies is not as reliable a method as PCR testing. ZIKV has been isolated in blood, urine, semen, tears, saliva, and amniotic fluid; however, the infectivity of these fluids is not known.[42,44,66]

In women who are pregnant or who plan to become pregnant, the current CDC recommendations are that both neutralizing IgM and RT-PCR tests be sent, and if both are negative, a plaque reduction neutralization test should be performed to confirm a negative diagnosis.

Treatment

Treatment for MERS

First-line treatment for MERS is supportive. For patients with dehydration or signs of sepsis, fluid resuscitation is indicated, according to usual practice. Antibiotics are warranted if concomitant bacterial infection is suspected.

Currently, there is no good animal model for studying MERS treatment, so additional treatment options are based on case series or extrapolation from other illnesses, such as SARS. In vitro, multiple antiviral agents have activity against MERS, including interferon, ribavirin, protease inhibitors, nitazoxanide, teicoplanin, and mycophenolate mofetil.[67,68] In a case series, 8 patients survived after receiving a combination of mycophenolate mofetil and interferon, although the severity of illness in these patients was lower than in other large cohorts.[69]

Treatment for CHIKV Infection

Although several targets for therapeutic agents have been proposed based on molecular process studies, no specific treatment exists. Opioids are an option for pain control during acute infection. A host of different classes of drugs have shown some in vitro efficacy against CHIKV but have yet to be evaluated in vivo.[70] General supportive measures include analgesics and antipyretics. Intravenous fluids can be administered for dehydration. A short course of corticosteroids can be considered in the ED for pain control in conjunction with nonsteroidal anti-inflammatory drugs (NSAIDs) for patients with chronic joint pain, but these patients should be referred to a rheumatologist for further management.

Treatment for ZIKV Infection

Acetaminophen is preferred initially until severe dengue is ruled out. NSAIDs can be administered after the patient has been afebrile for at least 48 hours. All women of childbearing age must have a pregnancy test performed in addition to asking whether she is pregnant or planning to become pregnant. If the pregnancy test is positive, it is important to estimate the time of pregnancy by last menstrual period and quantitative human chorionic gonadotropin (hCG) testing. If relevant, fetal heart tones may be reassuring; however, no specific emergent intervention or procedure is indicated in the ED in the absence of any acute threat to the pregnancy. Counseling with specialists from obstetrics and infectious disease should be arranged.

Special Populations

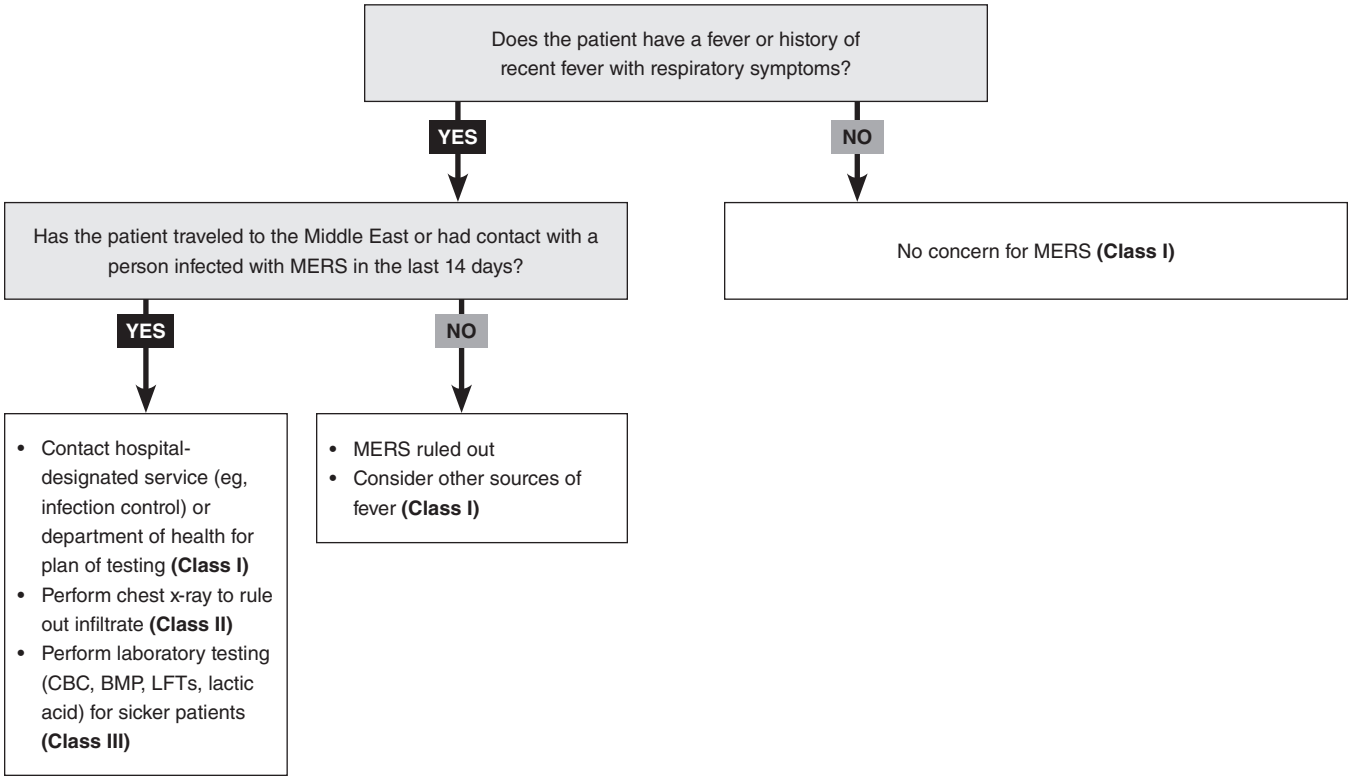
CHIKV Infection in Pregnant Women and in Children

CHIKV infections are not more severe among pregnant women, although there have been reports of miscarriages.[23] Most pregnant women with CHIKV infection have no long-term sequelae either for themselves or their children. However, neonates born to mothers with high viremic loads suffered severe neurologic and cardiac complications, with subsequent neurocognitive delays and death occurring during large CHIKV outbreaks.[22,23] CHIKV infection in older children is usually benign, and the associated arthritis is better tolerated. When complications in children occur, a higher prevalence of neurological and dermatologic manifestations are reported.[71]

ZIKV Infection in Pregnant Women

Given the association and concern for vertical transmission and congenital defects, including microcephaly, ophthalmologic abnormalities, and other possible sequelae as yet unknown even in apparently well live births, pregnant women who are traveling to endemic areas should be strongly advised to avoid mosquitos and wear insect repellent. The risk of congenital defects is believed to be highest when exposure occurs in the first trimester, and much lower or nonexistent for acute infections that occur in the second and third trimester. Pregnant patients with suspected or confirmed ZIKV infection should be referred to an obstetrician specializing in high-risk pregnancies, for serial ultrasounds and monitoring for congenital anomalies.[72,73] In the case of a negative pregnancy test in a patient who is found to be positive for ZIKV, it is important to advise the patient to use appropriate birth control for at least 8 weeks. In male patients with positive ZIKV tests, caution and appropriate birth control should be practiced for at least 6 months.

Clinical Pathway for Management of Suspected Middle East Respiratory Syndrome



Abbreviations: BMP, basic metabolic panel; CBC, complete blood cell count; LFT, liver function test; MERS, Middle East respiratory syndrome.

Class of Evidence Definitions

Each action in the clinical pathways section of *Emergency Medicine Practice* receives a score based on the following definitions.

Class I
- Always acceptable, safe
- Definitely useful
- Proven in both efficacy and effectiveness

Level of Evidence:
- One or more large prospective studies are present (with rare exceptions)
- High-quality meta-analyses
- Study results consistently positive and compelling

Class II
- Safe, acceptable
- Probably useful

Level of Evidence:
- Generally higher levels of evidence
- Nonrandomized or retrospective studies: historic, cohort, or case control studies
- Less robust randomized controlled trials
- Results consistently positive

Class III
- May be acceptable
- Possibly useful
- Considered optional or alternative treatments

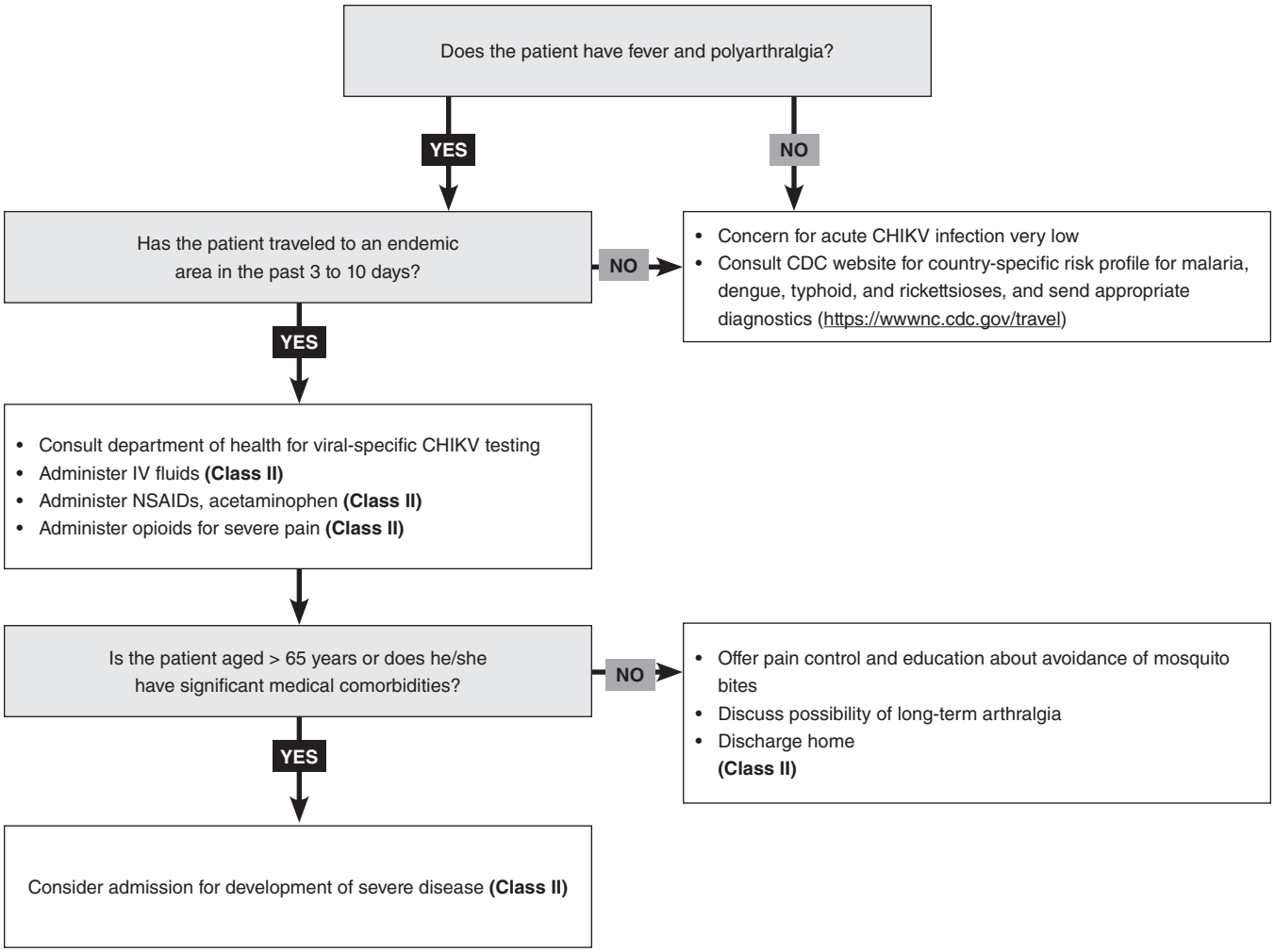
Level of Evidence:
- Generally lower or intermediate levels of evidence
- Case series, animal studies, consensus panels
- Occasionally positive results

Indeterminate
- Continuing area of research
- No recommendations until further research

Level of Evidence:
- Evidence not available
- Higher studies in progress
- Results inconsistent, contradictory
- Results not compelling

This clinical pathway is intended to supplement, rather than substitute for, professional judgment and may be changed depending upon a patient's individual needs. Failure to comply with this pathway does not represent a breach of the standard of care.

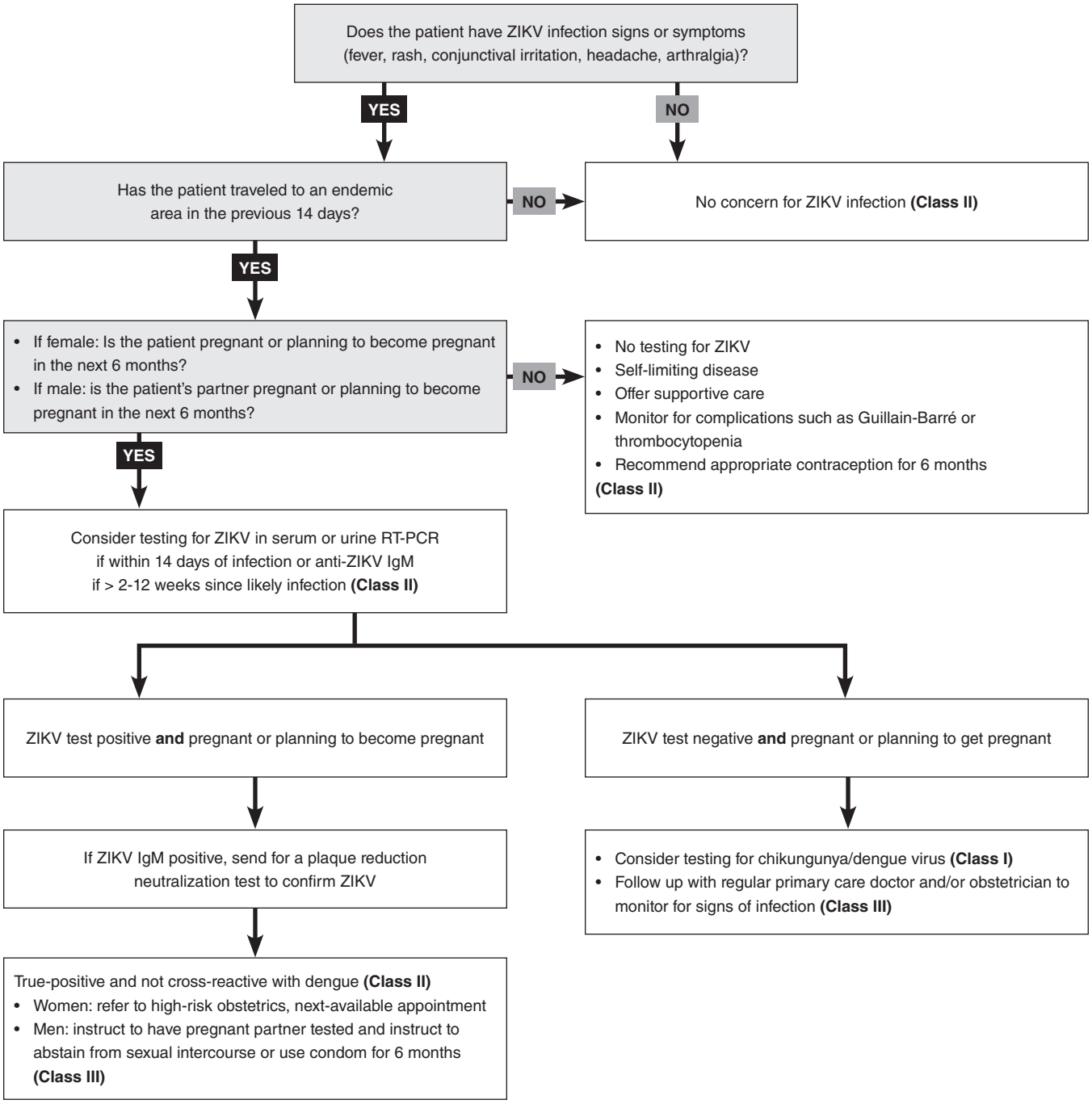
Clinical Pathway for Management of Suspected Chikungunya Virus Infection



Abbreviations: CDC, United States Centers for Disease Control and Prevention; CHIKV, chikungunya virus; IV, intravenous; NSAID, nonsteroidal anti-inflammatory drug.

For Class of Evidence definitions, see page 10.

Clinical Pathway for Management of Suspected Zika Virus Infection



Abbreviations: IgM, immunoglobulin M; RT-PCR, reverse transcription polymerase chain reaction; ZIKV, Zika virus.
For Class of Evidence definitions, see page 10.

Controversies and Cutting Edge

MERS

Vaccine development is underway for MERS using immunoglobulin G (IgG) antibodies isolated from survivors of the infection. Currently, there are 2 vaccines developed but not yet in clinical trials.[7,74] The use of plasma from survivors of MERS has been considered as a treatment modality, based on improved survival of patients with SARS who received convalescent plasma.[68] However, given the small number of donors available, plasma treatment for MERS has not been evaluated extensively.[75]

CHIKV Infection

Several vaccines for CHIKV infection have been under development since the 1970s.[76] Although there is no currently licensed vaccine available for prevention, several have shown promise in preclinical studies. Two recent phase 1 vaccine trials with a live recombinant measles-based CHIKV vaccine and a virus-like particle CHIKV vaccine showed good immunogenicity and safety.[77,78] A phase 2 clinical trial with a live attenuated virus was shown to be highly immunogenic but, likely due to lack of interest/funding, was not studied further.[79] A streamlined molecular assay to simultaneously detect and differentiate among CHIKV, ZIKA, and dengue infection has been developed and holds promise for quickly making a diagnosis in the acute phase of infection.[80]

ZIKV Infection

While there is currently no vaccine for ZIKV, projections are for a vaccine to be developed in 1 to 5 years. It is important to note that these projections were made when ZIKV infection was still considered by the WHO to be a public health emergency of global concern, which is no longer the case. Accordingly, a de-escalation of research and vaccine development is likely to occur.[81,82]

In terms of treatment and cure for ZIKV infection, repurposing screens for drugs approved by the United States Food and Drug Administration (FDA) have shown some effect against the virus, though none have been approved by the FDA for treatment of ZIKV infection. Some molecular mechanisms that show promise for possible targets for drug action include pan-caspase inhibitors and cyclin-dependent kinases (CDKs) that inhibit ZIKV replication.[46]

Disposition

Disposition for Patients With MERS

Admission criteria for a patient with MERS or suspected MERS is similar to any other respiratory or viral illness. Clear indications for admission include hypoxia, dehydration requiring intravenous fluids or electrolyte repletion, or multiorgan dysfunction. In a study examining risk factors for mortality in 1291 patients with MERS, multivariate analysis showed that older age and the presence of comorbidities increased the risk of mortality.[8] Therefore, the emergency provider should strongly consider admitting these patients with higher mortality risk. If a patient with MERS is discharged from the ED, it is critical that providers inform patients, their families, caregivers, and contacts about the possibility of transmission of this disease through droplets and fomites. Providers should also encourage isolation, as much as possible, in the home environment in addition to the use of respiratory masks. If the clinical suspicion for MERS is high and the results of PCR testing are not immediately available, providers should instruct these patients to remain on home isolation until conclusive testing is complete.

Disposition for Patients With CHIKV Infection

For CHIKV infection, most patients aged < 65 years without any other significant comorbidities can be safely discharged home with adequate pain control. Patients with renal failure, cardiopulmonary effects, or meningoencephalitis need to be admitted. Incapacitating pain might require admission for pain control. Admission is also required if ruling out hemorrhagic complications of dengue or severe malaria. Consider admission for patients aged > 65 years with diabetes, coronary artery disease, or chronic respiratory diseases. Counsel patients to avoid becoming bitten by mosquitos during the first week of illness to reduce the spread of the infection. Lastly, educate the patient on possible chronic joint symptoms requiring long-term management under the care of a rheumatologist.

Disposition for Patients With ZIKV Infection

The vast majority of ZIKV infections are asymptomatic or mildly symptomatic, and thus nearly all patients can be safely discharged home with outpatient follow-up and with instructions to monitor for neurologic or other sequelae. No isolation measures are needed for ZIKV-infected patients; however, patients should be instructed on the prevention of further spread of the disease, to avoid mosquitos, use mosquito repellent (safe in pregnancy), and to consider abstinence or condom use to avoid sexual transmission. Pregnant patients with ZIKV infection should receive urgent referral to high-risk obstetric care. Patients with presentations consistent with severe neurologic sequelae (eg, Guillain-Barré syndrome, encephalitis) should be admitted to the applicable intensive care unit. ZIKV-induced Guillain-Barré syndrome has been found to have a quicker progression and shorter plateau than other causes of this syndrome.

Summary

It is critical for emergency clinicians to be aware of current infectious disease outbreaks on the international spectrum. Make use of the extensive resources of departments of health, the CDC, WHO, and other international organizations to stay informed. A complete travel history is critical to the successful diagnosis of the returning-traveler patient, and understanding the full spectrum and course of each disease is important for appropriate screening, testing and disposition, including advising patients on measures to take to prevent local spread of these diseases.

Time- and Cost-Effective Strategies

- Order dengue titers and malaria peripheral smears in the beginning of the patient assessment to rule out these infections early in the course of acute illness.
- Avoid unnecessary radiographs of joints, as these will yield very little information that will change your management.
- Avoid joint aspirations in CHIKV patients unless only a single joint is involved and suspicion for septic joint is high.

Risk Management Pitfalls for Managing Emerging Infectious Diseases

(Continued on page 15)

1. **"I knew he had a respiratory virus, but I did not think to take a travel history."**
   In patients with fever, the differential diagnosis changes based on the travel history. For patients who might have MERS, for example, it is critical to identify whether the patient traveled to a region with active disease or came in contact with someone who was sick or in that region. If the appropriate history is not obtained, a MERS patient will not receive a mask or be placed in isolation, which increases the chance that the infection will spread to others.

2. **"The patient looked pretty good to me, and even though she was older, I didn't think she needed additional testing."**
   Severe disease is less common, but patients at risk for more severe disease and mortality as a result of MERS are those who are elderly and have medical comorbidities. Therefore, in these patients, it is prudent to assess for evidence of more severe infection through diagnostic studies (eg, renal function, lactic acid).

3. **"I suspected that this patient had MERS because he had traveled to Saudi Arabia. The lung sounds were coarse and his oxygen saturation was 94%, but I thought it was OK to discharge him without a chest radiograph since there is no treatment available anyway."**
   The presence of hypoxia and abnormal lung sounds suggests that this person may have more severe disease than MERS. The clinical spectrum of MERS varies from very minor illness to ARDS and multiorgan dysfunction. Patients who are hypoxic and/or who have abnormal lung sounds should have a chest radiograph to exclude more severe disease requiring hospitalization.

4. **"I was fairly certain that my patient did not have dengue, so I gave her ibuprofen for her joint pains. I never suspected chikungunya; actually, I had never heard of it."**
   Considerable overlap in symptoms occurs for dengue and chikungunya. The distinguishing feature of chikungunya is fever and polyarthralgias, but in early acute disease, this might be difficult to determine. In very ill travelers returning from regions with chikungunya and dengue, it is important to rule out dengue infection and refrain from giving NSAIDs initially to reduce the possibility of hemorrhagic complications.

5. **"The patient had a fever initially, but she looked really well and had a history of arthritis. I treated her with acetaminophen, she felt better, and I sent her home without any further testing. She went to her doctor 2 weeks later, and her doctor sent out tests for chikungunya. Now, the department of health just called me inquiring about this patient because she tested positive and there are more patients diagnosed with CHIKV infection in the county where she lives."**
   With increased global travel, emergency clinicians should obtain a travel history on all patients presenting to the ED with symptoms of an infection and consider the possibility of vector-borne illnesses, regardless of the severity of presentation. Checking with the department of health and educating the patient on avoiding mosquito bites will improve surveillance and prevent local spread of disease.

- Consider performing a lumbar puncture to rule out bacterial meningitis in patients presenting with severe neurologic symptoms.
- Speak with an infectious disease specialist or your local department of health to discuss additional laboratory tests needed to confirm the diagnosis.
- Ensure that your ED has a protocol in place to follow up on results that return after the patient has been discharged.

Case Conclusions

After obtaining the patient's travel history, your first patient was given a mask to wear and moved from the regular ED cubicle into an isolation room under droplet exposure precautions. Staff in the ED were informed about the concern for a possible case of MERS and reminded to take strict precautions and use personal protective equipment when evaluating this patient. Further interview findings confirmed that the patient was at risk for MERS based on recent travel to Saudi Arabia 1 week prior (given that the MERS incubation period is between 5 and 12 days and screening is recommended for those who have

Risk Management Pitfalls for Managing Emerging Infectious Diseases

(Continued from page 14)

6. **"The patient's mother told me that there was no malaria in the region where she had traveled, and she convinced me that she had CHIKV infection because all of her family members had this recently. The patient felt a little better after ibuprofen, and I sent her home to follow up with her pediatrician. She came back the same day and is now in the ICU."**
   Failure to consider the possibility of malaria in patients with a fever and recent travel can be calamitous. Malaria is endemic in many parts of the world, and those infected with *Plasmodium falciparum*, particularly children, suffer significant morbidity and mortality if left untreated. Always consider malaria in febrile travelers and obtain parasite blood smears when applicable.

7. **"The patient that I sent home yesterday with chikungunya came back today with renal failure. She was a vigorous 66-year-old who had well-managed diabetes and chronic obstructive pulmonary disease, and excellent outpatient follow-up. Her creatinine was only slightly elevated at the time that I saw her. I can't believe she got worse."**
   Most patients with CHIKV infection have a mild febrile illness and recover without difficulties. Patients aged > 65 years and those with significant comorbidities have a greater risk of severe illness. Strongly consider admitting these patients for observation for further complications.

8. **"His family said he was not acting himself, but he was older and had a fever. I admitted him to the floor, but he probably could have been discharged at that point. I certainly did not expect him to get transferred to the ICU!"**
   Although it is a rare complication of ZIKV infection, subtle signs of encephalitis, such as mild confusion, warrant closer monitoring. A lumbar puncture and thorough evaluation for other complications, such as thrombocytopenia, should be considered as well.

9. **"She had a typical story for ZIKV, and the urine pregnancy test was negative in the ED. I didn't see the need to discuss the risk of congenital syndrome."**
   Although there is no need for any specific intervention or procedure in the ED, all women of child-bearing age should be counseled regarding the risk of congenital abnormalities. Even if they are not currently pregnant, the patient may become pregnant during her infection. All pregnant women should be monitored by a high-risk pregnancy obstetrician and an infectious disease specialist.

10. **"He was complaining of mild weakness in his legs, but his vitals looked great and he was very well-appearing, so I thought he was probably just having the typical arthralgias. Even if this was ZIKV infection, it's a self-limiting viral syndrome, after all."**
    ZIKV infection has been associated with a higher incidence of Guillain-Barré syndrome, and subtle complaints of weakness should be investigated thoroughly. Although it is still being studied, ZIKV-induced Guillain-Barré syndrome is thought to progress faster than if induced by other causes, though time to recovery also tends to be shorter.

returned within 2 weeks). The patient had no significant medical history. Because of the finding of an abnormal lung examination, you obtained a chest radiograph, which did not show an infiltrate. The infectious disease consultant recommended contacting the department of health, which advised testing the patient for MERS and other ED patients possibly exposed prior to his placement in the isolation room. You obtained nasopharyngeal secretions for PCR testing. On reassessment, the patient was more dyspneic, demonstrated increased respiratory effort, and had an oxygen saturation of 92% on room air, which led to the decision to admit him to the hospital in a respiratory isolation room. His PCR test result was later shown to be positive. The patient had an uncomplicated hospital course and was discharged to home isolation.

For your second patient, you consulted the CDC website and learned that all areas in the Dominican Republic (except for Santiago and Santo Domingo) posed a threat for malaria infection in United States travelers. The website informed you of a recent outbreak of CHIKV infections in the town where the patient worked, and noted its common clinical presentation. You ordered parasite peripheral blood smears and dengue titers. You called the local department of health to discuss the case, and they recommended additional blood tests to confirm the diagnosis. A few hours later, you told the patient that her blood tests, including dengue titers and malaria screen, were normal and that you strongly suspected a chikungunya infection. You informed her that additional testing for CHIKV was sent to the department of health for confirmation, and that they would contact her with the results. In the meantime, you educated her about preventing any mosquito bites for the next few days to avoid spreading CHIKV to the local mosquito population and risking a local outbreak of the disease. You discharged her with prescriptions for acetaminophen and ibuprofen and a referral to follow up with her primary care provider.

Your third patient had a positive pregnancy test, and she stated that her last menstrual period was about 7 weeks ago. She denied any vaginal bleeding or pain, and her bedside ultrasound confirmed an intrauterine pregnancy. Her fever and headache improved and she felt better after treatment with acetaminophen. You explained the likelihood of her diagnosis of ZIKV infection and discussed the possibility of birth defects and the need to follow up with a high-risk pregnancy obstetrician and infectious disease specialist as soon as possible. After having a discussion with the obstetrician on call, you discharged the patient with a follow-up visit at the high-risk pregnancy clinic in 2 days.

References

Evidence-based medicine requires a critical appraisal of the literature based upon study methodology and number of subjects. Not all references are equally robust. The findings of a large, prospective, randomized, and blinded trial should carry more weight than a case report.

To help the reader judge the strength of each reference, pertinent information about the study, such as the type of study and the number of patients in the study is included in bold type following the references, where available. The most informative references cited in this paper, as determined by the author, are noted by an asterisk (*) next to the number of the reference.

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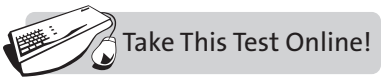
CME Questions



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1. MERS belongs to which genus of virus?
a. *Alphavirus*
b. *Coronavirus*
c. *Flavivirus*
d. *Metapneumovirus*

2. Which of the following statements about Zika, MERS, and chikungunya is TRUE?
a. They are all RNA viruses.
b. They are all transmitted by the bite of an infected mosquito.
c. The first outbreaks were identified in the 1950s.
d. Persistent neurocognitive delays are a common feature.

3. Outside of Saudi Arabia, where has the other largest outbreak of MERS infection taken place?
a. Iraq
b. Brazil
c. South Korea
d. Yemen

4. The most common complication of CHIKV infection is:
a. Chronic arthralgias
b. Guillain-Barré syndrome
c. Iritis
d. Meningitis

5. What is the preferred laboratory test for identification of MERS infection?
a. IgM antibody testing
b. White blood cell testing for leukopenia
c. Nasal aspirate for polymerase chain reaction (PCR)
d. Viral culture

6. All of the following laboratory findings may help to diagnose CHIKV infection EXCEPT:
a. Abnormal liver function tests
b. Hypocalcemia
c. Lymphopenia
d. Thrombocytopenia

7. Which of these viruses is most likely to cause a false-positive in a serum ZIKV IgM antibody test?
a. CHIKV
b. Dengue virus
c. MERS coronavirus
d. Yellow fever virus

8. Reverse transcription PCR testing can be used to detect ZIKV in which of the following bodily fluids?
a. Cerebrospinal fluid
b. Serum
c. Urine
d. All of the above

9. A 42-year-old man is admitted to the hospital on isolation for active MERS infection. Which of the following is currently the standard treatment?
a. Broad-spectrum antibiotics
b. Interferon
c. Plasma of MERS survivor
d. Supportive care

10. Which of the following drugs should be avoided in a patient with suspected ZIKV?
a. Acetaminophen
b. Cephalexin
c. Ibuprofen
d. Ondansetron

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- Shoulder Injuries
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Target Audience: This enduring material is designed for emergency medicine physicians, physician assistants, nurse practitioners, and residents.

Goals: Upon completion of this activity, you should be able to: (1) demonstrate medical decision-making based on the strongest clinical evidence; (2) cost-effectively diagnose and treat the most critical presentations; and (3) describe the most common medicolegal pitfalls for each topic covered.

Learning Objectives: Upon completion of this article, you should be able to: (1) Identify the appropriate travel history that puts a patient at risk for MERS, CHIKV, or ZIKV; (2) describe the most common presenting symptoms of MERS, CHIKV, and ZIKV; (3) identify the most appropriate diagnostic testing modalities for MERS, CHIKV, and ZIKV; and (4) identify which patients with suspected cases of MERS, CHIKV, or ZIKA require admission and which can be safely discharged from the emergency department.

Discussion of Investigational Information: As part of the journal, faculty may be presenting investigational information about pharmaceutical products that is outside Food and Drug Administration-approved labeling. Information presented as part of this activity is intended solely as continuing medical education and is not intended to promote off-label use of any pharmaceutical product.

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