Recognition and Management of Infectious Biothreats and Emerging Pathogens

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KEYWORDS

• Biothreats • Emerging pathogens • Bioterror agents • Critical care

KEY POINTS

- For a myriad of reasons, it is essential that the frontline critical care clinician be aware of various syndromes caused by emerging and reemerging infectious biothreats.
- Critical care clinicians should be familiar with the identify–isolate–inform–initiation of care algorithm.
- While travel and symptom screening are important, it is equally important to remember that pathogens may also present in patients with nontraditional exposures.
- Infection prevention and control practices vary depending on modes of transmission of specific pathogens or pathogen families.
- A febrile patient from a malaria-endemic region has malaria until proven otherwise.

INTRODUCTION

Emerging infectious diseases are caused by pathogens that have newly appeared in a population or have previously existed but appear to be rapidly increasing in incidence and geographic range. The concept of biothreat—which has expanded to include emerging infectious disease—originally referred to biological pathogens or the substances produced by them (ie, toxins) used to deliberately cause disease or harm to humans. Many biothreat agents are often also designated by the US government as select agents, subject to strict regulations regarding possession and use, due to their potential to cause significant disruption to political and socioeconomic arenas and thus posing a risk to national security and public health.

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Abbreviations	
AIIR	airborne infection isolation room
CDC	Centers for Disease Control
ECMO	extracorporeal membrane oxygenation
HPS	hantavirus pulmonary syndrome
ICU	intensive care unit
MERS-CoV	Middle East respiratory syndrome coronavirus
MODS	multiorgan dysfunction syndrome
SARS-CoV	severe acute respiratory syndrome coronavirus
VHF	viral hemorrhagic fever

These pathogens, which cause high-consequence infectious diseases, are highly infectious, may be highly communicable, and are highly hazardous. Infectivity can be measured by the infectious dose needed to infect 50% of a given population (also known as the ID_{50} or LD_{50}, for *lethal* dose), with the lower the number the smaller the amount of organism or toxin needed to cause infection and thus the greater the infectivity. Communicability, or transmissibility, is measured by how many potential secondary infections an infected person can cause—this is quantified by the reproductive number R_0, with the higher the number the more transmissible a pathogen. Lastly, hazard is measured by mortality and, in an outbreak, the case fatality ratio. Often, these pathogens have limited medical countermeasures, and because of that, may have great ability to spread within and without the community, causing severe disease, requiring enhanced and coordinated health care worker, health care system, and public health responses. Recognition by critical care clinicians is crucial, as the first detection of an event will likely occur upon presentation to a facility with resulting admission to a critical care unit.[1,2]

This brief article will provide a concise summary that includes an overview of the general approach to emerging pathogens, the epidemiology, presenting signs and symptoms, clinical course and medical management, as well as infection prevention and control measures to be taken (**Figs. 1** and **2**).

SELECT INFECTIOUS BIOTHREATS

Viral Hemorrhagic Fevers

Viral hemorrhagic fevers (VHFs) are globally widespread and caused by viruses found within several different families. VHFs are considered category A bioterror agents, are zoonotic in origin, and unfortunately not all transmission vectors and/or reservoirs have been identified. Incubation period from exposure to development of symptoms may be up to 21 days, with an average of 5 to 14 days.[3] Symptoms are initially nonspecific and may include acute onset of fever, cephalalgia, myalgias, gastrointestinal symptoms, and rash. Depending on the specific pathogen there may be unique features, but nevertheless the initial stage is often referred to as the *dry* stage. As disease progresses, patients may develop "wet" symptoms including massive fluid losses (can be up to and beyond 10 L/day) from diarrhea or emesis, hemorrhage from multiple sites, shock, and multiorgan dysfunction syndrome (MODS). In this phase, death is common, and mortality rates depending on the specific infection can range from 20% to 100%.[3,4] The classic hemorrhagic symptoms may not always be present but may often be subtle including ecchymoses at multiple sites, petechiae, conjunctival hemorrhages. The disease course itself can last up to 4 weeks or longer, and several hemorrhagic fever viruses have been shown to persist in immunosenescent areas of the body (ocular tissues, gonads) for years (filoviruses in particular).[5]

Virus Family	Illness Caused	Common Geography	Vector or Source	Person-to-person spread	Precautions	PPE	Comments
Filoviridae	Ebola Virus Disease	Central, sub-Saharan Africa	? Presumed bat	YES	Contact, Droplet/Airborne, Eye		Dry phase = impermeable gown to mid-calf Wet phase = Full body coverage
	Marburg virus		Fruit bat				
Arenaviridae	Lassa fever	West Africa	Rodents	YES	Contact, Droplet/Airborne, Eye		Dry phase = impermeable gown to mid-calf Wet phase = full body coverage
	Junín Machupo (Bolivian HF) Guanarito (Venezuelan HF) Sabia (Brazilian HF)	South America					
Bunyaviridae	CCHF – Crimean Congo Hemorrhagic Fever	Europe, Mediterranean, Middle East, Africa, India, China	Tick, infected livestock	YES	Contact, Droplet/Airborne, Eye		Dry phase = impermeable gown to mid-calf Wet phase = Full body coverage
	Hantaviruses (HPS/HFRS*) (Sin Nombre, Andes virus)	Worldwide	Rodent	Possible	Standard Precautions unless Andes virus suspected		Contact, Droplet/Airborne, Eye for potential Andes virus or contact/clean-up of rodent droppings
	Rift Valley Fever	All of sub-Saharan Africa	Mosquito	No	Standard Precautions		
Flaviviridae	Yellow Fever	Tropics	Mosquito	Blood [1]	Standard Precautions		[1] Potential risk of Yellow Fever transmission in blood transfusion, or immediately post vaccination
	Dengue	Tropics	Mosquito	No			
	Kyanasur	India	Tick	No			
	Omsk	Siberia					

HPS* - Hantavirus Pulmonary Syndrome HFRS* - Hemorrhagic Fever with Renal Syndrome

Yellow Fever - [1] Transmission of the vaccine strain of Yellow Fever can occur thru blood transfusion and breastmilk. Blood donation & breastfeeding should be avoided for 2 weeks after vaccination.

Fig. 1. Transmission based precautions for select emerging infections with primary modes of transmission via contact. (National Emerging Special Pathogens Training and Education Center. (2024). Viral Hemorrhagic Fevers (VHFs) PPE Matrix. NETEC Resource Library. Retrieved 2026-03-24, from https://repository.netecweb.org/items/show/1693.)

Virus Family		Pathogen & Illness	Common Geography	Vector/Source	PPE	Comments
Coronaviridae		Middle East respiratory syndrome coronavirus (MERS-CoV) MERS	Arabian Peninsula	Unknown. Found in camels and humans	Respirator, eye protection, gown, and gloves	Airborne infection isolation room when available
		Severe acute respiratory syndrome associated coronavirus (SARS-CoV-1) SARS	Asia	Possibly bat and civet	Respirator, eye protection, gown, and gloves	Airborne infection isolation room when available HHS Select Agent
Orthomyxoviridae		Influenzas (highly pathogenic) Influenza	Global	Human, bird, pig, cattle; other species possible	Respirator, eye protection, gown, and gloves	Special handling of culture material may be required
Paramyxoviridae	Henipavirus genus	Nipah virus (NiV)	Asia, Bangladesh, India	Fruit bats, pigs	Respirator, eye protection, gown, and gloves	Category A waste, HHS Select Agent
		Hendra virus (HeV)	Australia	Flying fox, horses	Respirator, eye protection, gown, and gloves	Category A waste, HHS Select Agent
		Langya (LayV)	China	Possibly Shrews	Respirator, eye protection, gown, and gloves	Waste is not currently listed as Category A waste but would expect it to be if cases reoccur
		Measles (Rubeola) *morbillivirus*	Global	Humans	Respirator, eye protection, gown, and gloves	Contagious 4d prior to appearance of rash. Airborne infection isolation - strict
		Mumps	Global	Humans	Mask, eye protection, gloves	Pre- and asymptomatic spread possible
		Human metapneumovirus	Global	Humans	Mask, eye protection, gloves	
Orthopox		Mpox Clade 1 historically more severe Clade 2 wide circulation since 2022	West and Central Africa: sustained transmission. Global	Multiple animal species, humans	Respirator, eye protection, gown, and gloves	Culture material only of Clade 1 requires special handling as Category A waste
		Variola major - smallpox	Eradicated worldwide 1980	Humans	Respirator, eye protection, gown, and gloves	Any case would be considered terroristic or lab accident related. Category A and Select Agent

Fig. 2. Transmission based precautions for select emerging infections with primary modes of transmission through the air. (National Emerging Special Pathogens Training and Education Center. (2024). Viral Hemorrhagic Fevers (VHFs) PPE Matrix. NETEC Resource Library. Retrieved 2026-03-24, from https://repository.netecweb.org/items/show/1693.)

Targeted medical countermeasures against most VHFs are limited. Effective vaccines exist for one species of Ebolavirus, and there are several promising candidates for other pathogens. Similarly, monoclonal antibody therapy cocktails are approved for Zaire Ebolavirus and are in clinical trials for other hemorrhagic fevers—these latter may be obtained via investigational new drug mechanisms via US federal pathways (Table 1). Diagnosis is usually by reverse transcription-polymerase chain reaction (RT-PCR) syndromic testing at specialized laboratories, as these pathogens require rigorous biosafety level 4 precautions. Additionally, enzyme-linked immunoassays, viral culture, and immunohistochemistry may be performed, but their utility in acute outbreaks may be limited. With respect to treatment, only measure that has been consistently shown to improve mortality in these patients is early, optimized supportive critical care that includes management of potential bacterial and parasitic coinfections (ie, bacterial sepsis and malaria). Mortality has been shown to increase by 11%/day from symptom onset to initiation of early supportive care. Proper identification of these patients through symptom and travel screening, along with appropriate infection prevention and control measures, are essential to protecting patients, health care workers, and hospital systems.[3,4] Dengue, which can cause a hemorrhagic fever in its severe form, will be discussed later.

Anthrax

Anthrax is arguably the most likely bioterrorist or biological weapons scenario to occur and it has been successfully deployed in such a manner. In the wake of the events on September 11, 2001 in the United States, spores of *Bacillus anthracis* were sent, in an act of bioterrorism, through the mail resulting in 22 cases of anthrax, 5 of which were fatal. Anthrax is caused by *B anthracis*, a gram-positive spore-forming bacillus. There are 4 potential types of infection in humans depending on the route of exposure: cutaneous, inhalational, gastrointestinal, and injectional. The cutaneous form is the most common and least lethal, beginning as a pruritic papule evolving to a vesicle and then to a painless coal-black eschar associated with edema and lymphadenopathy. It can occasionally disseminate.[6]

Table 1
Select viral hemorrhagic fever medical countermeasures

Select Viral Hemorrhagic Fever	Licensed Preventative Medical Countermeasure	Licensed Therapeutic Medical Countermeasure
Ebola virus (Orthoebola virus zairense)	Yes	Yes REGN (Inmazeb); MAb114 (Ebanga)
Sudan virus (Orthoebola virus sudanense)	In development	In development MBP134
Marburg virus	In development	In development BCX4430 (Galidesivir); MBP091
Lassa virus	In development	No [Ribavirin]
Junin virus	Yes	No
Crimean–Congo hemorrhagic fever virus	In development	No [Ribavirin]
Nipah virus	In development	In development MBP1F5
Kyasanur forest disease	Yes	No

Source World Health Organization. International Clinical Trials Registry Platform (ICTRP). Available at: https://trialsearch.who.int/. Accessed September 8, 2025.

The inhalational form is most lethal and the form that would follow an intentional aerosol release resulting in a critically ill patient. The incubation period of inhalational anthrax can vary from 1 day to 6 weeks, with the onset of illness consisting of nonspecific symptoms characteristic of influenza-like illnesses, but importantly without rhinorrhea. Rapid progression to severe respiratory distress and shock occurs with evident hemorrhagic mediastinitis (identified as mediastinal widening and pleural effusions on chest X-ray or computed-tomography [CT] scans). It is important to be aware that over 50% of cases will have neurologic involvement that can manifest as meningitis.[6,7] Laboratory confirmation can be performed via blood culture (70% sensitive) or via cerebrospinal fluid (CSF), pleural, and vesicular fluid. Biopsy and polymerase chain reaction (PCR) are sensitive but not widely available, and serology is not useful early in the course of illness. Systemic anthrax is a toxin-mediated disease and therapy should include antimicrobials with anti-toxin activity. Empiric therapy consists of combination antimicrobials including a fluoroquinolone plus linezolid plus meropenem (for potential central nervous system [CNS] involvement) and a fluoroquinolone plus linezolid or clindamycin if meningitis has been ruled out. Minimum therapy duration is 2 to 3 weeks along with adjunctive steroids if meningitis present.[7] Additionally, adjunctive anti-toxin monoclonal and polyclonal antibody-based therapy exists as single dose administration, though supplies are limited and would need to be obtained in consultation with local and federal partners.[8,9] It is also critical to drain any fluid collections that may be present such as pleural, pericardial, and ascitic—such collections should be considered to be empyema-like—as it confers a clinical benefit. There is no person–person transmission, and standard infection prevention precautions are sufficient.[7]

Smallpox

Smallpox is caused by variola virus, of which the most common clinical form is variola major. Highly transmissible via droplet or aerosols, smallpox has an overall mortality of approximately 30%. Classic features include high fevers and a disseminated centrifugal rash that displays a synchronized progression of macules, papules, vesicles, and pustules. The incubation period may be 10 to 14 days, and patients are considered contagious until all lesions have completely healed over.[10] The differential diagnosis includes disseminated primary varicella, disseminated herpes simplex virus (HSV), and severe mpox.[10,11] Diagnosis may be made via serologic testing, culture of lesions, PCR, and electron microscopy, though clinical suspicion remains essential. While the mainstay of treatment is supportive, proper infection prevention and control measures (including airborne and contact isolation, and potentially high-level containment) are essential.[10] Close contacts need to be closely surveilled and quarantined. Several approved therapeutic medical countermeasures exist, including tecovirimat and brincidofovir, as well as vaccinia immune globulin.[10,12,13] Additionally, two effective vaccines, one nonreplicating and one live, are approved for use.[14] In recent years, another orthopox virus caused disease, mpox has emerged worldwide and is an important condition to also consider given the clinical similarity in the presentation (albeit with a lower mortality rate).

Pneumonic Plague

Plague is caused by *Yersinia pestis*, an aerobic gram-negative bacillus, and is a zoonotic infection of domestic and wild animals of which humans are incidental hosts. However, it can spread human-to-human through inhalation of contaminated aerosols and is highly contagious. Primary pneumonic plague has an incubation period of 1 to 3 days after inhalation or droplet transmission from another infected person, while

secondary pneumonic plague develops in approximately 10% of patients as a result of hematogenous spread from bubonic or septicemic forms.[15] The disease is characterized by the sudden onset of dyspnea, high fever, pleuritic chest pain, and hemoptysis leading to respiratory failure and shock. Diagnosis is often clinical but confirmed by culture; while rapid antigen tests exist in some endemic regions, none are approved for use in the United States—though the Western United States is a plague-endemic area in which approximately a dozen cases per year are reported. Appropriate and early antimicrobial therapy is essential and recommended with gentamicin, a fluoroquinolone, or doxycycline. For severe disease combination therapy is recommended for 14 days. Pneumonic plague is fatal unless antimicrobial therapy is begun within the first day of illness.[15,16]

Tularemia

Colloquially known as rabbit fever, tularemia is caused by the gram-negative coccobacillus known as *Francisella tularensis*. Several forms exist (pneumonic, typhoidal, ulceroglandular, and oculoglandular), and natural transmission of tularemia can occur through infected mosquitos, ticks, or rabbits. In summer months in the northern hemisphere this illness is sometimes diagnosed in landscapers, construction workers, and groundskeepers. An intentional release would likely cause pneumonic tularemia, with a mortality rate of 2% to 24%.[17] With an incubation period of 3 to 5 days, symptoms resemble severe community-acquired pneumonia that can rapidly progress to septic shock, acute respiratory distress syndrome and respiratory collapse. Diagnosis requires enriched culture media, serology, immunofluorescence testing, or PCR, though laboratory personnel must be alerted to the potential pathogen to ensure proper biosafety precautions. Treatment is with an aminoglycoside, a fluoroquinolone, or doxycycline. Standard precautions are adequate as there is no human-to-human transmission.[17]

Botulism

Caused by the deadliest toxin known to humankind, botulism is caused by toxin release from the gram-positive spore forming *Clostridium botulinum.* There are 8 known toxin types (zinc endopeptidases) and by binding selectively and irreversibly to proteins at the presynaptic membrane the toxins prevent release of acetylcholine, causing flaccid paralysis. The 6 most common presentations include: infantile, wound, gastrointestinal, iatrogenic, inhalational, and foodborne. The main challenge with botulism is that the toxin is colorless and odorless when in gaseous form as would be anticipated from an intentional release. Six hours post-exposure to aerosolized botulinum toxin, a symmetric descending paralysis occurs with cranial nerve dysfunction (that may include diplopia, dysphagia, pupillary dilation, and ptosis) and progression to rapid respiratory failure. Importantly, fever and altered mental status may be absent. Importantly, facial paralysis may obscure clinical distress and because patients may not be hypoxic until late stages of disease, any signs of respiratory compromise should prompt consideration of inhalational botulism and early intubation. In fact, the intubation rate is approximately 50%.[18]

Diagnosis is largely clinical though confirmatory tests do exist, albeit with significant delays. Culture may take up to 3 weeks, mouse bioassays may detect the toxin within 48 hours, and PCR detection may occur. However, early optimized critical care is the mainstay of treatment coupled with antitoxin and if suspicion is present, administration of antitoxin is vital. Equine-derived heptavalent (toxin A–G) botulinum antitoxin is the primary medical countermeasure, obtained from the US Centers for Disease Control (CDC). In a deliberate attack, the human-derived bivalent antitoxin BabyBIG should not be administered as it can only counteract toxins A and B.[18]

Dengue

Arboviruses are viruses that spread to humans through arthropod vectors (such as mosquitoes and ticks). Some cause VHFs and others typically occur during warm weather when specific vectors are more active. Diseases with the potential to lead to critical illness include dengue fever, yellow fever, Oropouche virus, chikungunya, and various encephalitic infections such as eastern equine encephalitis or West Nile virus. Infected mosquitos, specifically *Aedes aegypti*, are the main vector for several of these viruses, and due to climate change and intercontinental travel, their range has significantly expanded. Direct human-to-human transmission does not occur. Travel and symptom screens are essential to guide testing and management.

Dengue, spread by Aedes mosquitoes and maintained naturally in a sylvatic cycle with nonhuman primates, continues to become endemic in more countries in the Northern and Western hemispheres. There are four major serotypes and three clinical syndromes as defined by the World Health Organization and Pan-American Health Organization: dengue without warning signs (fever, retro-orbital headache, severe bone pain (*break-bone fever*), myalgias, maculopapular rash, and nausea/vomiting); dengue with warning signs (sustained abdominal pain, persistent vomiting, edema, mucosal bleeding, lethargy, hypotension, hepatomegaly, and increasing hematocrit); and severe dengue (shock or respiratory distress, severe bleeding, and organ failure).[15] More serious forms of infection may occur following initial resolution of fever, and hemorrhagic fever may include neurologic involvement. Severe dengue is a manifestation of antibody-enhanced infection in which antibodies generated during a prior infection with one serotype enhance infection by another. Values show leukopenia, thrombocytopenia, and elevated transaminases. Diagnosis can be made via serology or RT-PCR. Treatment for each form of dengue fever is supportive. Given gastrointestinal and hematologic effects, non-steroidal anti-inflammatory drugs (NSAIDs) are to be avoided; oral rehydration (if able) or with isotonic fluids is strongly encouraged, and systemic glucocorticoids are also to be avoided in patients with severe dengue, including patients with shock.[19]

It is important to note that in the United States, Dengue is common in American Samoa, Puerto Rico, the US Virgin Islands, the Federated States of Micronesia, the Republic of Mashall Islands, and the Republic of Palau. Local transmission of dengue has occurred in Hawaii, Texas, New York and Florida—areas where the requisite mosquito is present. It is also important to note that, until recently as of this writing, there was a safe, and effective live-attenuated vaccine, Dengvaxia, that provided significant protection against the four serotypes of the virus but was limited in its use, for safety reasons, to those with serologic evidence of prior infection and above the age of 6. It remains available in over 100 countries but not in all regions where endemic, and due to declining demand will no longer be produced. Other vaccine candidates are in advanced stages of research and one, Qdenga, is licensed in many countries.[20]

Hantaviruses

There are greater than 20 known species of hantaviruses, a genus of single-stranded RNA viruses belonging to the Bunyaviridae family. Transmitted primarily through contact with infected rodent bodily fluids or feces, they cause two diseases. Those found in the Western Hemisphere are known as *New World* hantaviruses and are causative agents of hantavirus pulmonary syndrome (HPS); hantaviruses found in Europe and Asia are known as *Old World* hantaviruses and cause hemorrhagic fever with renal syndrome. The viruses infect many species of rodents, especially the white-footed mouse, without causing visible disease.[21] Importantly, 1 species of hantavirus found in South

America, Andes virus, can spread from person to person.[22] HPS, the major form of hantavirus disease has an incubation period of 1 to 8 weeks (median 14–17 days) after exposure to rodent excreta and initially may present similar to an influenza-like illness that rapidly progresses to high fever, bilateral diffuse interstitial edema, and respiratory compromise requiring oxygen supplementation within 72 hours of hospitalization, all in a previously healthy person. This stage can last from 7 to 10 days and is also characterized by a rapidly progressive thrombocytopenia, hemoconcentration, left shift, and immunoblasts greater than 10% of total lymphocytes. Chest radiographs show pulmonary edema, and mortality is close to 40%.[21,23] Diagnosis often relies on a combination of exposure history, serology, and RT-PCR. A classic example is that of a young, otherwise healthy person with outdoor exposure or to that of rodents who presents with rapidly progressive respiratory failure in an endemic area of the United States (eg, New Mexico). Optimized, supportive critical care therapy is essential, and patients with cardiogenic shock should be considered early for extracorporeal membrane oxygenation (ECMO), as this may increase survival significantly.[24] Droplet and contact precautions (preferably in an airborne infection isolation room, or AIIR) are essential, though, with the exception of Andes virus, human-to-human transmission has not been documented (see **Fig. 1**). Those who survive to the convalescent phase at 7 to 10 days will likely have complete recovery in 2 to 3 weeks.[21,23]

Influenza

There are two principle types of influenza viruses: influenza A and B and both can cause acute respiratory viral infections that causes seasonal epidemics, and infrequent global pandemics that occur with major antigenic changes of the virus and from spillover from animal reservoirs (such as swine or birds). As respiratory viruses, transmission between humans occurs primarily through the air via coughing and sneezing, with an incubation period of between 1 and 4 days (1–2 day average). Influenza can cause a spectrum of illness from mild to life-threatening. Symptom onset is typically rapid with fever, nonproductive cough, myalgias, chills, malaise, sore throat, and nasal congestion. Gastrointestinal symptoms are not typically part of the syndrome seen in adults but can be seen in children.[25] As the disease progresses, respiratory symptoms become the primary issue; cough may be present for several weeks. Older adults and those immunosuppressed may not present with typical signs and symptoms but may also have altered mental status, anorexia, malaise, weakness, and dizziness. Aside from pulmonary crackles or decreased airflow, physical exam findings are largely absent, but leukocytosis and leukopenia may be present, and radiographic imaging may show bilateral reticular or reticulonodular opacities with or without consolidations. Ground glass opacities may be seen on CT scan as well.[25]

Complications include viral pneumonia and secondary bacterial pneumonia. Viral pneumonia, especially in immunocompromized individuals or those with comorbidities can rapidly lead to acute respiratory distress syndrome (ARDS). Secondary bacterial pneumonia complicates approximately 0.5% of cases in healthy young individuals and 2.5% in older individuals or those immunosuppressed; it typically arises within a few days of influenza onset. Classically, there is a period of improvement for a few days but then worsening of fever, cough, sputum production, and consolidation. Most often, organisms isolated include *S. pneumoniae, H. influenzae, S. aureus*, and less commonly, *Aspergillus* spp. Influenza can also lead to neurologic complications, myositis, myocarditis, pericarditis, renal failure, and MODS.[26]

The virus is usually easily isolated from nasal or throat specimens, sputum, or tracheal secretions within the first 3 days of illness, yet a lower respiratory tract sample

is preferred. Neuraminidase inhibitors such as oral oseltamivir, IV peramivir, the selective endonuclease inhibitor baloxavir, and inhaled and/or IV zanamivir (investigational use only), are all active against influenza A and B viruses, though resistance is rising. While the greatest morbidity and mortality benefit occurs with initiation of therapy within 72 hours of symptoms, any patient admitted to the intensive care unit (ICU) should receive antiviral therapy, typically combination therapy as well as immunomodulation. In 2017 and again in 2021, the combination of naproxen–clarithromycin–oseltamivir was found to reduce both 30- and 90-day mortality rates as well as lengths of stay in both adult and pediatric patients with severe influenza A infections and is currently recommended as a potential treatment option in severe cases.[27,28] In addition to treating potential co-imposed or superimposed bacterial infections, supportive critical care is warranted, including ventilatory support and potential ECMO initiation when indicated.[25,26]

The potential for zoonotic avian or swine influenza viruses should also be considered, especially with severe disease in a person with epidemiologically significant animal exposures. The treatment principles, however, remain the same. Of the myriad avian influenza viruses that have infected humans, the H5N1 strain is unique in its ability to infect multiple mammalian species. Human cases have accrued with varying degrees of severity, possibly clade dependent, but human-to-human transmission appears severely constrained.

Coronaviruses

Though coronaviruses have circulated on the planet for hundreds if not thousands of years, with most responsible for common mild seasonal respiratory infections, there are several important human and animal pathogens that have caused significant disease in the 12th century. Severe acute respiratory syndrome coronavirus 1 and 2 (SARS-CoV-1 and SARS-CoV-2), were responsible for the SARS outbreak in 2002 to 2004 and the coronavirus diseases 2019 (COVID-19) pandemic from 2020 to 2023, respectively.[29,30] The Middle East respiratory syndrome coronavirus (MERS-CoV) causes MERS and can similarly lead to life-threatening disease.[31] However, these three coronaviruses cause a spectrum of disease in which the care of hospitalized versus nonhospitalized patients is quite different. For SARS-CoV-1 and SARS-CoV-2, acute viral pneumonia can lead to acute respiratory distress syndrome. Incubation period is generally within 14 days, and for SARS-CoV-2, nasopharyngeal samples either through rapid antigen testing or PCR have good sensitivity.[32] Severe or critical illness is characterized by hypoxemia, tachypnea, and bilateral pulmonary infiltrates. Respiratory failure, septic shock, and multisystem organ failure are hallmarks of critical illness. Optimized, supportive, critical care is essential. For all hypoxemic patients with SARS-CoV-2 infection, supplemental oxygen (either invasive or noninvasive) should be initiated for oxygen saturation goals greater than 90% with avoidance of hyperoxia. If able, prone ventilation has been shown to be beneficial, and if patients fail noninvasive measures, intubation should be performed using clinical discretion.[33] Remdesivir and dexamethasone, in the setting of patients with evident radiographic findings of infection and oxygen requirements, have been shown to be beneficial. In patients with severe disease, tocilizumab and baricitinib have been shown to have adjunctive benefit as well for immunomodulation.[33] It is also important to note that a hypercoagulable state is often present, and patients are at risk for venous and pulmonary emboli, coronary occlusion, and myocardial infarctions. For refractory hypoxemia, ECMO is also an effective modality.[33] Patients should be cared for using droplet and contact precautions. Time to recovery for COVID-19 is variable and dependent on comorbidities and severity of disease, and patients often have prolonged lingering systemic affects.

Of note, outpatient oral antivirals (nirmatrelvir/ritonavir and molnupiravir) as well as a pre-exposure monoclonal antibody for the immunocompromized (pemivibart) are also available medical countermeasures.

MERS was first identified in Saudi Arabia in 2012, and all subsequent cases have been linked to the Arabian Peninsula. The virus is a zoonosis found in humans usually with exposure to dromedary camels, though there have been cases of human-to-human transmission (mostly in health care and household settings) and cases with unclear epidemiologic linkages.[31] Cases can range from asymptomatic states to severe ARDS and death. Most patients present with fever, cough, and dyspnea. Leukopenia, lymphopenia or lymphocytosis, thrombocytopenia, and elevated lactate dehydrogenase (LDH) levels are possible. Lung imaging findings range from minimal to extensive bronchovascular markings, opacities, interstitial changes, and consolidations. Diagnostic tests ideally should be run on lower respiratory tract samples, as well as upper tract and serum samples. Real-time reverse transcription-polymerase chain reaction (rRT-PCR) testing may be performed at specialized laboratories as can serology, though with limited sensitivity and specificity. MERS is considered a high-consequence infectious disease (similar to VHFs) and it is of paramount importance to properly identify (through travel, exposure, and symptom screening) and isolate patients, as treatment is strictly supportive; there are no known medical countermeasures. At a minimum, patients should be placed in AIIRs with additional contact precautions and ideally cared for in a high-level containment unit. Estimated mortality rate is approximately 35% (see **Fig. 2**).[34]

Malaria

No overview of emerging or re-emerging infectious threats would be complete without mention of malaria. Unfortunately, this parasite is regaining footholds in regions from which it has previously been eradicated, and local transmission without prerequisite travel history and exposure is occurring in the southern regions of the northern hemisphere. *Anopheles* mosquitoes are the primary vector for malarial parasites, and of the 5 species of *Plasmodium*, *P. falciparum, P. knowlesi,* and *P. vivax* commonly cause severe disease.[35] Rarely, zoonotic Plasmodium species can also cause human disease. Incubation periods may be up to 30 to 35 days though symptoms typically will appear within the first 2 weeks following infection. Typical symptoms include fever, chills, headache, myalgias, arthralgias, hepatosplenomegaly, jaundice, vomiting, diarrhea, and rash. Severe malaria can rapidly occur in patients if timely treatment is not initiated. Clinical criteria for severe cases (confirmed malaria with organ dysfunction) include one or more of: altered mentation, seizures, prostration, acidosis, hypoglycemia, normocytic anemia less than 5 g/dL (in adults), acute renal failure, jaundice, pulmonary edema, disseminated intravascular coagulation (DIC) with bleeding, shock, hyperparasitemia greater than 10%. Coinfections with gram-negative organisms (commonly *Salmonella typhi*, or enteric fever) frequently occur.[36]

The diagnosis is established with consistent symptoms and positive rapid diagnostic testing, either through antigen testing confirmed via blood smears or PCR. When clinical concern is present, however, testing should not delay early initiation of empiric therapy given the potential for rapid deterioration. Aggressive supportive care including oxygen supplementation and potentially mechanical ventilation, vasopressor support, and renal replacement therapy are often needed. For those with altered mentation, a lumbar puncture should be performed (if safe) to rule out bacterial meningitis. Intravenous or intramuscular artesunate therapy is

preferred for initial therapy of adult patients with severe disease regardless of malarial species. When artesunate is not available, oral artemether-lumefantrine, oral atovaquone-proguanil, oral quinine, or oral mefloquine may be acceptable. The level of parasitemia is checked every 12 hours until the parasitemia level falls below 1% and/or through the initial course of artesunate. Once this improvement is documented and the patient is tolerating oral substances, the treatment with an oral regimen can be continued, depending on the species. Subsequently parasitemia should be monitored on a daily basis until it becomes negative. Steroids and exchange transfusions are no longer recommended as targeted therapies for malaria itself.[37]

As a matter of principle, a fever in a traveler returning from an endemic malarial region has malaria until proven otherwise. Malaria testing should also be part of the diagnostic workup in a critically ill patient with fever of unknown origin, regardless of exposure history. This last point is important given that recent years have shown autochthonous transmission of malaria in the continental United States (Florida, Maryland, and Texas) as the requisite vector species exists in many areas of the United States and malaria was only eliminated from the country in the 1950s.

DISCUSSION

The most critical part of recognition and treatment of an infectious biothreat or emerging infectious disease is a proactive clinical approach that anticipates such a diagnosis due to factors that might include: unusual exposures, occupation, travel, and other epidemiologic factors. Vector exposure and consideration of climate factors are important in identifying potential risks for patients. One vector not discussed here in depth is that of ticks, which can transmit multiple infections including rickettsial and protozoal infections as well as VHFs (such as Crimean–Congo hemorrhagic fever). This highlights the importance of a good exposure history and the use of family collateral information. The identify–isolate–inform algorithm with early intervention with aggressive supportive critical care is incredibly important. If concerning signals are discovered through a symptom and travel/exposure screen, patients should be quickly isolated and subsequent care performed with appropriate transmission-based personal protective equipment. Lastly, appropriate local, state and regional agencies and experts should be notified to provide guidance and logistical support on determination of additional steps.[38]

Proactivity would involve engagement with the microbiology laboratory to determine the appropriate acquisition and packaging of samples, appropriate diagnostic testing sequence, and the need for reference laboratory resources. In many cases, the diagnosis of an emerging infectious disease comes late in the course of illness when treatment may be less effective. However, with the advent of more sophisticated and sensitive microbiologic diagnostic modalities the time that elapses before one exhausts potential common etiologies is increasingly being shortened, facilitating the proactive approach we advocate.

One area which may be of higher yield is in patients who have sepsis, septic shock, and severe pneumonia in which standard diagnostic testing has not yet yielded a specific microbiological diagnosis. In these critical illness situations, it is (in the authors' view) crucial that the culprit etiologic agent is discovered not only for treatment purposes but also because it may have epidemiologic import. For example, the recent melioidosis cases in the United States linked to aromatherapy products. Even in fatal cases, a microbiological investigation postmortem may yield important information that is actionable from a public health perspective.

Background

Melioidosis is a serious bacterial infection caused by *Burkholderia pseudomallei*. The pathogen is typically found in soil and water in tropical/subtropical regions (eg, Southeast Asia, northern Australia). It is rare in the continental United States, and when it does occur, it is often linked to travel to endemic areas.

Detection of the outbreak

In 2021, US public health officials identified a cluster of four melioidosis cases in four different states: Kansas, Minnesota, Texas, and Georgia. None of the infected individuals had traveled internationally.

The illness onset for these cases occurred over roughly a 5-month span. Symptoms varied; in some cases, there was dyspnea, in others fever and mental status changes. Three of the 4 patients required ICU level care and two died. In all cases, melioidosis was not on the differential diagnosis of treating clinicians but only diagnosed based on routine microbiological studies. Two of the four case patients were children. The adult patients both experienced sepsis, with one in frank septic shock. Both adult patients demonstrated CT evidence of pneumonia and were bacteremic.

Investigation and source identification

Public health authorities, including the CDC, initiated an epidemiologic and laboratory investigation. They collected environmental and product samples from the homes of affected people, seeking a common exposure source.

A breakthrough came when a bottle of Better Homes and Gardens Lavender and Chamomile Essential Oil Infused Aromatherapy Room Spray with Gemstones was found in the home of the Georgia patient. That bottle tested positive for *B pseudomallei*. Genetic testing showed that the bacterial strain in the spray matched that which infected all four patients. This established a direct link between the contaminated product and the outbreak.

The product was imported from India, a country where *B pseudomallei* is endemic.

Significance and Implications

- This represented a rare instance of nontravel associated melioidosis, which presented to hospitals with undifferentiated sepsis syndromes
- Highlights diagnostic challenges: nonspecific symptoms, passive diagnosis via routine microbiological studies
- Concretizes the real risk for emerging infectious diseases to present to ICUs cloaked as an ordinary common infectious disease syndrome

Case Study: Melioidosis Outbreak via Aromatherapy Spray (United States, 2021). Reference: Gee JE, Bower WA, Kunkel A, et al. Multistate outbreak of Meliodosis associated with imported aromatherapy spray. N Engl J Med. 2022 Mar 3; 386(9):861-868.

In recent years, the concept of disease X has become an important consideration when preparing for emerging infectious diseases. Disease X is best understood as a placeholder concept to subsume any unknown pathogen that causes severe disease.[39] As such, the proactive approach is critical to identify any disease X pathogen that may be causing disease. In this context, it is essential that proactivity extend from diagnostic and treatment considerations to include infection control procedures. Such procedures would include the preemptive and appropriate level of isolation of patients until an etiologic agent is identified. In cases in which VHF or other high consequence infectious disease is suspected, a special biocontainment unit may be employed.

SUMMARY

As air travel continues to increase, shipping continues and migratory mammal ranges extend, emerging and reemerging infections will continue to spillover at an ever-increasing rate into human populations. Often the first recognition of an event may be in a patient's presentation to an ICU. It is crucial that, especially in cases in which diagnosis is unclear, detailed travel, exposure, and symptom history is obtained coupled with thorough physical exams to potentially elucidate clues. This is part of the identify–isolate–inform–intervene algorithm, and when coupled with an understanding of the hierarchy of controls, in which PPE plays a crucial role, can lead to better outcomes among patients. It is also important that the critical care physician or provider have an understanding of the potential infections or vectors that may be present in countries from which returning travelers may present or know where to obtain the information, as well as high-yield clinical syndromes in which early targeted therapy can be life-saving.

CLINICS CARE POINTS

- A detailed travel and exposure history and symptom assessment is essential for the early identification of patients with emerging pathogens, especially when the diagnosis may be unclear.
- Practice the early application of the identify-isolate-inform-intervene algorithm.
- A basica understanding of current pathogen outbreaks and the knowledge on where to find information is essential for proper management.
- A febrile patient from a malaria-endemic region has malaria until proven otherwise.
- An understanding of varying infection prevention and control practices is important in keeping staff and patients safe.

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