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Biothreat Agents and Emerging Infectious Disease in the Emergency Department

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KEYWORDS

• Emerging infectious disease • Bioterrorism • Biosecurity • Biothreats
• Health security

KEY POINTS

- An astute emergency medicine clinician can minimize the cascading effects of an infectious disease emergency.
- The use of diagnostic tools to make a specific diagnosis is key.
- Early infectious disease consultation is advised with any uncertainty.

INTRODUCTION

Emergency physicians in every location in the world, in developed and developing countries alike, will undoubtedly be confronted with the possibility of an emerging infectious disease in their career. A subset of these physicians may be faced with a patient who has potentially been exposed to biological weapons. Of the myriad infectious disease emergencies an emergency physician contends with, these 2 possibilities are the gravest and most impactful. In such scenarios, the emergency department (ED) clinician can be the key in recognizing or containing an outbreak.

The challenge inherent with emerging infectious diseases presenting in the ED is that such cases can be camouflaged, lurking amongst innumerable infectious disease clinical syndromes, from common colds to viral rashes. This article provides guidance to emergency physicians as to how to approach this challenging problem as well as familiarizing readers with specific microbial threats of high consequence.

DEVELOPING A GENERAL APPROACH

A key method for detecting the presence of an emerging infectious disease syndrome or a biological weapons exposure in an ED patient is to develop a general approach

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that seeks out key historical and physical examination clues. This approach is not different from what is included in a full history and physical examination but requires meticulous attention to certain aspects of the history.

Travel History and Situational Awareness

Travel history becomes a key focus of the history because many infectious diseases, especially of the emerging variety, have delimited borders in which they are prevalent. The travel history must be coupled, however, with situational awareness as to what infections are known to be present in specific parts of the world. Such a task is daunting for most physicians and, therefore, it is important that they know where such resources can be found. Both the Centers for Disease Control and Prevention (CDC) (www.cdc.gov/travel) and ProMED (Program for Monitoring Emerging Diseases) (www.promedmail.org) are 2 such resources that are easy to access and continually updated. Using these resources, a busy provider can quickly assess which specific infection risks any given country might confer.

An important component of the travel history is understanding the dates of travel and how they relate to the incubation period of specific infections. Travel must be contextualized and integrated with incubation period, because domestic infections acquired before or after travel might be mistaken for a travel-related infection.

Additionally, EDs in a given geographic locale (eg, metropolitan area, county, or state) should develop a mechanism to have insight into changes in ED volume, chief complaint mix, and unusual diagnoses at other EDs in the region. Much of this can be accomplished through leveraging emergency health care coalitions and local or state health departments to develop tools to enhance insight into the vicissitudes of a given region's ED-relevant infectious disease problems through syndromic surveillance programs.

Exposure History

An important component of an individual's risk for particular infections is related to exposures. Attention must be paid to animal exposures (domestic and wild), eating habits, occupation, and hobbies. Additionally, it is essential to determine if a person has had any sick contacts or has attended a mass gathering, because an ED physician might be seeing one of the first formal presentations of a wider outbreak.

SPECIFIC AGENTS

Of the specific biological agents, the category A agents (anthrax, plague, tularemia, and botulism), and certain viral hemorrhagic fevers (VHFs) (eg, Ebola, Marburg, Machupo, and Lassa fever) are of the highest priority. **Table 1** provides salient points regarding the treatment of the category A biothreat agents.

In all cases of uncertainty, prompt consultation with an infectious disease physician is recommended.

Anthrax

Anthrax is caused by the gram-positive bacillus, *Bacillus anthracis*. It is a ubiquitous spore-forming gram-positive bacterium that is found naturally in the soil worldwide. It is a disease of herbivores. Humans can contract 1 of 4 forms of the infection: cutaneous, inhalational, injectional, and gastrointestinal.[1,2] Of these forms, cutaneous is by far the most common and represents a majority of cases.[3] An intentional release of anthrax is expected to result in primarily inhalational cases.[1] Anthrax is not contagious from person to person and no special precautions are required.[4]

Table 1
Treatment and prophylaxis of category A agents

Agent	Typical Incubation Period	Treatment	Prophylaxis
Anthrax (meningitis not excluded)	1–7 d	Ciprofloxacin, 500 mg IV q12h; linezolid, 600 mg IV q12h; and meropenem, 1 g IV q8h, plus antitoxin therapy	Vaccine + ciprofloxacin, 500 mg PO BID, or doxycycline, 100 mg PO BID
Tularemia	3–5 d	Gentamicin, 5 mg/kg IV q24h	Ciprofloxacin, 500 mg PO BID, or doxycycline, 100 mg PO BID
Plague	1–3 d	Gentamicin, 5 mg/kg IV q24h	Ciprofloxacin, 500 mg PO BID, or doxycycline, 100 mg PO BID
Botulism	12–72 h	Heptavalent antitoxin	
Smallpox	12–14 d	Vaccine	Vaccine

Cutaneous anthrax is characterized by a painless black ulceration (Fig. 1) that occurs on the site of exposure. Infection is more common in those exposed to animal products contaminated with spores, such as meat, drum skins, or wool. After an incubation period of approximately 7 days, the lesion characteristically begins as a papule and progresses to a black eschar. Diagnosis is often clinical, although culture, biopsy, polymerase chain reaction (PCR), and serology confirm the diagnosis. Mortality is low if the disease is recognized and treated with appropriate antimicrobials. Treatment regimens include oral ciprofloxacin or doxycycline (although penicillin may be used if susceptibility is known) for 7 days. If exposure was through a biological attack, treatment duration is extended to 60 days to cover incubating spores that may have been inhaled. Injectional anthrax has been exclusively linked to use of contaminated illicit drugs whereas gastrointestinal anthrax is due to ingestion of contaminated food.[3,4]

Fig. 1. Painless black eschar of cutaneous anthrax. (*Courtesy of* Archil Navdarashvili, Centers for Disease Control and Prevention. Available at: https://phil.cdc.gov/Details.aspx?pid=19826.)

Inhalational anthrax is the deadliest form of anthrax and occurs on inhalation of as little as 1 spore. Anthrax was historically known as *wool sorter's disease* because of its linkage with the occupation of wool sorting, in which spores on sheep's wool became aerosolized. The disease is characterized not by pneumonia but by mediastinal widening (**Fig. 2**) that can progress rapidly to shock. Toxin-laden pleural effusions may be present. The disease begins after a week-long incubation period and is typically biphasic with flulike symptoms (with the notable exception of rhinorrhea) occurring before a terminal phase. When anthrax of any form progresses, the grave complication of hemorrhagic meningitis can occur.[3]

The treatment of systemic anthrax syndromes (inhalational, gastrointestinal, and injectional) involves first ruling out the presence or absence of meningitis via a lumbar puncture. If meningitis is confirmed or cannot be ruled out, the treatment regimen should include 3 central nervous system penetrating drugs, 1 of which should be a protein synthesis inhibitor (eg, linezolid) and 1 of which should be bactericidal (eg, meropenem). The third drug could be ciprofloxacin. If meningitis has been ruled out, ciprofloxacin and clindamycin or linezolid could be used for treatment (with de-escalation of ciprofloxacin to penicillin once drug susceptibility is known). Treatment is for 2 weeks to 3 weeks.[5] Adjunctive antibody therapies, available from the CDC, such as anthrax immune globulin, raxibacumab, and obiltoxaximab, also should be given.[5] Additionally, if present, pleural effusions, pericardial effusions, and ascites should be drained, a factor that has likely improved survival rates from inhalational anthrax in the modern era.[6]

Postexposure prophylaxis, for those exposed to anthrax spores, includes both an abbreviated 3-dose regimen of the vaccine coupled with 60 days of oral ciprofloxacin or doxycycline (antibody therapies can be used in this manner when no other prophylaxis method can be used).[3]

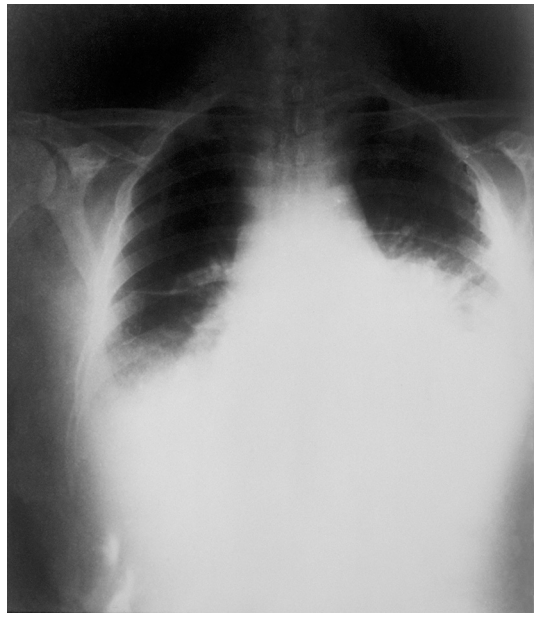

Fig. 2. Widened mediastinum secondary to inhalational anthrax. (*Courtesy of* Dr Philip S. Brachman, Centers for Disease Control and Prevention. Available at: https://phil.cdc.gov/Details.aspx?pid=1118.)

In a mass event the post-exposure prophylaxis regimen for adults can be shortened to 42 days after the first vaccine dose or 2 weeks after the last vaccine dose, which ever comes later.

Plague

Plague is caused by the gram-negative bacillus *Yesinia pestis* and is endemic in many parts of the world, including the Western United States. This zoonotic infection is naturally spread from rodents, such as prairie dogs, to humans via the bite of a flea. There are 3 forms of plague: bubonic (the most common), pneumonic, and septicemic. If used as a bioweapon, plague is expected to present in its pneumonic form.[7]

Bubonic plague is characterized by marked painful lymphadenopathy (**Fig. 3**) that develops after a 2-day to 6-day incubation period whereas pneumonic plague (**Fig. 4**) may be indistinguishable from ordinary community-acquired pneumonia but has a mortality rate that can reach 50%. Pneumonic plague has a 1-day to 3-day incubation period. Pneumonic plague is transmissible from person to person through respiratory droplets and requires patients be placed in droplet isolation.[3,7]

Diagnosis of pneumonic plague in an intentional attack requires a high index of suspicion and can be made through PCR, serology, and/or culture.[3,7]

The treatment of plague is with aminoglycoside antibiotics, such as gentamicin or streptomycin, for 7 days to 10 days, whereas postexposure prophylaxis of those exposed to an aerosol in a bioweapon attack consists of oral ciprofloxacin or doxycycline.[3,7]

Tularemia

Tularemia is caused by the gram-negative bacillus *Francisella tularenesis* and is naturally a zoonotic infection that is common in many parts of the United States. Naturally, tularemia may occur through tick, fly, and mosquito bites or through contact with reservoir animals (eg, rabbits). Contaminated uncooked food or water can also be a vehicle for spread. The most common presentation of tularemia is the ulceroglandular cutaneous form whereas a biologic attack likely results in pneumonic tularemia. Tularemia is not contagious between humans.[8]

Tularemia is notable for its low infectious dose in which inhalation of just a small number of bacilli can result in disease. Because of this, it is important to notify laboratory personnel about the possibility of tularemia, so they are able to don appropriate personal protective equipment when working with clinical specimens.[3,8]

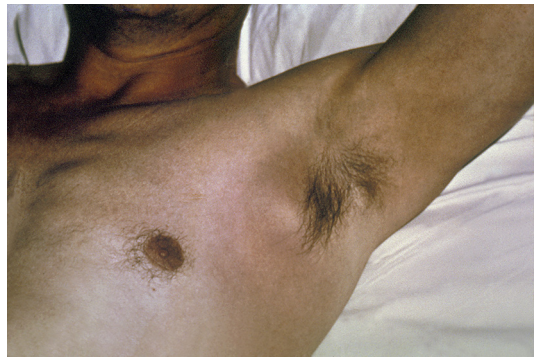

Fig. 3. Axillary bubo associated with plague. (*Courtesy of* Margaret Parsons and Dr Karl F. Meyer, Centers for Disease Control and Prevention. Available at: https://phil.cdc.gov/Details.aspx?pid=2061.)

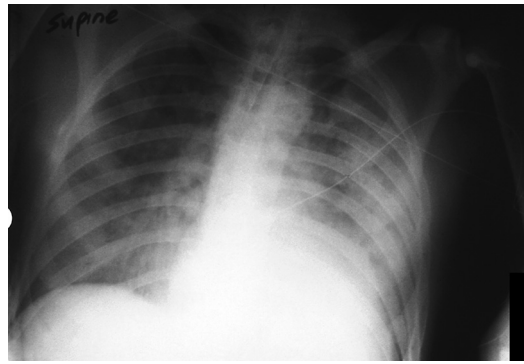

Fig. 4. Pneumonic plague. (*Courtesy of* Dr Jack Poland, Centers for Disease Control and Prevention. Available at: https://phil.cdc.gov/Details.aspx?pid=4079.)

Pneumonic tularemia occurs after a 3-day to 5-day incubation period and is essentially indistinguishable from community-acquired pneumonia. Even physicians who live in endemic areas often miss the diagnosis of tularemia in its various form, highlighting the need for tularemia to be in the differential diagnosis of compatible syndromes in endemic areas.[9] Temperature-pulse disassociation may be present and can serve as a clue to diagnosis.[8]

The treatment of tularemia is aminoglycoside antibiotics, such as gentamicin or streptomycin, for 7 days to 10 days. Postexposure prophylaxis, to those exposed to an aerosol in a biological weapons attack, is with oral doxycycline or ciprofloxacin.[3,8]

Botulism

Botulism is caused by the acetylcholine release-blocking neurotoxin released by *Clostridium botulinum*, a ubiquitous spore-forming gram-positive rod. There are several forms of naturally occurring botulism: infant, wound, and gastrointestinal. These forms result from exposure to spores of the bacteria, which then germinate and elaborate toxin. In a biological attack, inhalational botulism is expected, and it manifests similar to gastrointestinal botulism. Botulism is not contagious.[3,10]

After 12 hours to 36 hours postexposure to spores, clinical botulism occurs. It is characterized by a symmetric, flaccid, descending paralysis without sensory symptoms. Patients are afebrile and not tachycardic. Cranial neuropathies are common. Paralysis progresses to involve respiratory muscles and can be prolonged, requiring long durations of mechanical ventilation. Diagnosis is largely clinical. Confirmatory mouse bioassay testing is used to determine which of the several botulinum toxinotypes is responsible.[3,10]

Heptavalent antitoxin, which neutralizes toxinotypes A to G, is obtainable from the CDC and can neutralize toxin. Antibiotics and BabyBIG (California Department of Public Health, a bivalent botulinum antitoxin used in infant botulism) are not indicated.[3,10] There was controversy over the existence of an eighth toxinotype (H) but it has been shown to be a hybrid toxin and is neutralized by A-type antitoxin.[11] More recently, a toxinotype X has been described and is unable to be neutralized by any available antitoxin.[12]

Smallpox

Smallpox is the only human infectious disease that has been eradicated from the planet. As such, there is little current clinical experience with this disease. Smallpox

is a significantly contagious disease that is spread via airborne, respiratory droplet, or direct contact route. Fomites are also known to spread the virus.[3,13]

The clinical presentation of smallpox begins with flulike symptoms after a 14-day incubation period which is followed by the characteristic rash. The rash begins in a papular form and then progresses to umbilicated lesions and finally to pustules that crust and scab. A person with smallpox is contagious only from the appearance of the rash until the rash is scabbed, a key factor that led to its control.[3,13]

The rash of smallpox (**Fig. 5**) must be distinguished from similar rashes that can be seen with varicella. Several points of distinction are important. The rash of smallpox is centrifugal with more lesions on the face and extremities while the varicella rash is centripetal. The lesions of the smallpox rash are all at identical stages with identical appearances whereas the rash of varicella may have lesions of different stages. The case fatality rate of smallpox was historically 25%.[3,13]

A diagnosis of smallpox would be a national security emergency of the highest order because even 1 case represents either a laboratory accident or a biological attack. Because smallpox vaccination is no longer routine, there is a sizable amount of the world population that lacks immunity. Any suspicion of smallpox should prompt infectious disease consultation, airborne isolation procedures, and notification of local, state, and national public health authorities. The CDC has a telephone consultation service in place to discuss potential cases with experts.

A diagnosis of smallpox initially is based on clinical suspicion while confirmatory testing by PCR, viral culture, or electron microscopy is performed under appropriate biosafety conditions.[3,13]

There is no Food and Drug Administration–approved treatment of smallpox currently, although several experimental antiviral compounds are in late stages of clinical development and might be accessible. The smallpox vaccine is effective as postexposure prophylaxis, even during the incubation period, and should be given to all patient contacts, who also will be placed under public health surveillance. The vaccine is contraindicated in the immunosuppressed and pregnant and those with eczema. Experimental attenuated vaccines may be more suitable for these individuals.[14–16] Additionally, the smallpox vaccine carries a risk of myocarditis.[17]

Viral Hemorrhagic Fever

VHFs are caused by a diverse group of viruses, each with its own unique microbiological, epidemiologic, and clinical features. Of this group, which ranges from yellow fever

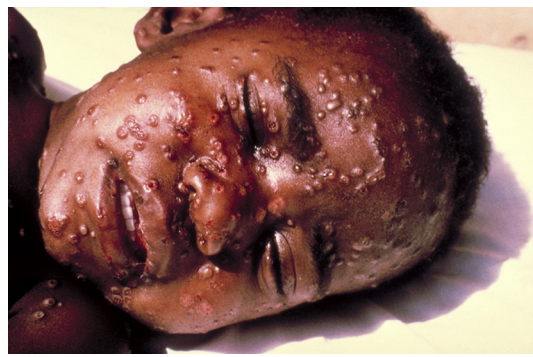

Fig. 5. Smallpox. (*Courtesy of* Centers for Disease Control and Prevention. Available at: https://phil.cdc.gov/Details.aspx?pid=3; with permission.)

to Ebola, certain are more important as potential biological weapons than others. In the biological weapons context, it is the filoviruses (Ebola and Marburg) as well as the arenaviruses (Lassa fever, Machupo, and others) that merit concern.

Despite their differences, this group of viruses is characterized by a clinical presentation that often includes general malaise, fever, rash, prostration, pharyngitis, nausea, vomiting, and diarrhea. Disease can rapidly progress to shock and multiple organ dysfunction syndrome with disseminated intravascular coagulation and hemorrhagic manifestations.[18]

Diagnosis can be made using molecular tests, but a high index of suspicion is needed to differentiate these infections from ordinary septic shock. In the ED patient, travel to endemic areas, exotic animal exposure, or laboratory work with VHFs might be the only clue to the etiology. In a biological attack, a cluster of patients with similar symptoms may present to several EDs in a given region. Any suspicion of a VHF should prompt immediate consultation with an infectious disease physician and state and local health authorities.[18]

Although these viruses are spread via blood and body fluid exposure and do not spread between humans via the airborne route, the experience of the United States during the 2014 West Africa Ebola outbreak has influenced infection control recommendations. The 2 nosocomial infections at a hospital in Texas have led to recommendations for strict airborne and body fluid isolation for patients suspected of having a VHF, with transfer to definitive care at specialized units for confirmed cases.[19]

Treatment is generally supportive and has proved life-saving in the case of Ebola. The recent experience with Ebola highlighted the fact that simple supportive care with fluids and electrolytes brought fatality rates down from 90% to less than 40%.[20] There are several experimental treatments and vaccines (which can be used for postexposure prophylaxis) that are available for filovirus infections and arenavirus infections that would likely be used in any domestic VHF cases caused by these groups of viruses.[21] For Ebola exposures, the experimental vaccine would be indicated for postexposure prophylaxis whereas a combination of experimental antiviral agents (eg, favipiravir) and antibody-based therapies, such as ZMapp, might be indicated after consultation with CDC. Lassa fever can be treated with intravenous ribavirin, which is available via CDC.

The possibility of VHF infection should be considered in those with severe illness and travel to areas in which these infections are endemic, such as parts of Africa (eg, Democratic Republic of Congo, Uganda, and Nigeria) or South America (eg, Brazil and Argentina). Consultation of the CDC travel Web site (www.cdc.gov/travel) is advised to determine specific VHF travel risks.

Middle East Respiratory Syndrome Coronavirus and Severe Acute Respiratory Syndrome Coronavirus

Coronaviruses (CoVs) are major causes of the common cold and rarely cause severe disease in immunocompetent hosts. There are, however, 2 CoVs that have the capacity to cause severe disease: severe acute respiratory syndrome (SARS)-CoV and Middle East respiratory syndrome (MERS)-CoV.

Although both SARS and MERS present to the ED as ordinary upper or lower respiratory tract infections, they have distinct geographic and epidemiologic features that should alert an ED physician to the possibility of their presence. SARS, which emerged in China in 2003, was a worldwide infectious disease emergency that led to more than 8000 cases worldwide, with approximately 10% of cases fatal—including in the United States. The virus was zoonotic in origin and linked to human consumption of palm civet cats. The spread of the virus was abetted by the presence of

superspreading events in which certain individuals infected a disproportionate number of others. The epidemic extinguished once infection control measures were instituted in health care settings and the consumption of palm civet cats ceased.[22]

MERS is also a zoonotic respiratory CoV that emerged in the Arabian Peninsula in 2012 and has been linked to contact with both bats and camels. All cases have an epidemiologic link to the Arabian Peninsula, including a multiple-ED superspreading event that occurred in South Korea. Mortality rates are approximately 30%.[22] In the United States, 2 imported mild cases have been diagnosed in travelers returning from the Middle East.[22]

MERS should be suspected in individuals with upper or lower respiratory infection after travel to the Middle East in the prior 2 weeks, and confirmatory molecular testing can be done in conjunction with state and local health authorities. Many respiratory viral panels have the capacity to identify the presence of a CoV and may be helpful in the work-up. Infectious disease consultation and institution of droplet or airborne precautions are advised.

There are no antivirals or vaccines available for any CoV.

Avian Influenza

Influenza is often considered one of the highest pandemic threats. Prior influenza pandemics have killed millions and have caused severe societal disruption. Each modern pandemic (1918, 1957, 1968, and 2009) has been linked to the emergence of a novel influenza A variant of zoonotic (avian, swine, or a combination) origin.

Zoonotic influenza viruses, in their first forays into humans, can cause a range of illness, ranging from ordinary influenza to fulminant disease, including pneumonia and acute respiratory distress syndrome. Poor to limited nonsustained human-to-human transmission characterizes these viruses in the prepandemic stage, with most cases linked directly or indirectly to poultry exposure. It is when sustained human-to-human transmission occurs that a pandemic is eminent.

Because of this threat, monitoring and surveillance efforts exist for avian influenza infections in humans and poultry. Currently, of the myriad zoonotic influenza infections, the H7N9 strain of influenza A has been deemed the highest threat amongst these viruses currently, although others (such as H5N1) are also important to track.[23]

The ED physician should suspect avian influenza in travelers from China and other areas in which avian influenza is known to circulate, who present within approximately 1 week after travel with upper or lower respiratory tract infection. Additionally, domestic agricultural workers or those with agricultural contact with flulike symptoms (eg, children at fairs) also may harbor zoonotic influenza infections.[24]

Diagnosis is similar to ordinary influenza, but a rapid or standard molecular test may or may not be able to detect influenza. Confirmatory testing is via health authorities. Treatment involves supportive care coupled to antiviral therapy with either oral oseltamivir or, if disease severity is high, intravenous peramivir. Infectious disease consultation and institution of droplet precautions is advised.

Emerging Arboviruses

Mosquito-borne arboviruses have increasingly taken on importance in the field of emerging infectious disease with the explosion of cases of West Nile, chikungunya, and Zika in the Western Hemisphere. Additionally, local transmission of dengue fever has occurred in Florida, Texas, Hawaii, and New York.[25,26]

Chikungunya, dengue fever, and Zika are all spread by the Aedes species of mosquitoes, which have habitats both within and outside the United States and cause clinically indistinguishable syndromes. These syndromes all involve fevers, rash,

myalgias, and arthralgias. Conjunctivitis has been noted with Zika. Prolonged debilitating arthralgias can occur with chikungunya whereas severe illness, including shock and hemorrhagic manifestations, can occur with dengue fever (especially with repeat infection with disparate strains).[27,28] Zika has been linked to Guillain-Barré syndrome and requires special counseling regarding sexual transmission and pregnancy given its ability to cause a devastating congenital syndrome.[29,30]

Travel history and residence in an endemic area (eg, Key West, Hawaii, and Texas) are important elements of the history. Diagnostic testing is commercially available for each infection.

Consultation with the CDC travel Web site is advised to assess specific risks for individual patients' travel history. No vaccines or antiviral therapies are available for these infections.

EMERGENCY MEDICINE AND SPECIFIC DIAGNOSIS

Emergency physicians play a crucial and unique role in the defense against emerging infectious disease and are most likely to encounter the first cases of any new infectious disease syndrome. The challenge that the emergency physician faces is that these cases do not announce themselves and are hidden among the sea of chief complaints that any ED sees on a given day.

With many clinical scenarios, a busy physician may not be inclined to pursue a specific diagnosis if it "doesn't change treatment," may lengthen ED length of stay, and will not produce a result while a patient is in the ED, creating follow-up logistical problems. Failing to diagnose an epidemiologically important emerging infectious disease or biological attack, however, can have tremendous cascading effects involving all sectors of society (health care, government, and economy) that can be minimized or averted with a proactive approach.

In the current era, there are several molecular multianalyte tests available, some of which are Clinical Laboratory Improvement Amendments (CLIA) waived and available at point of care for specific infectious disease syndromes, such as gastrointestinal infections, meningitis, and respiratory infections, that can be used to increase the rate of microbial specific diagnoses in ED settings. Biodefense cartridges, which probe for select bioagents, are also available. These tests, in the hands of an astute physician, can improve the nation's resiliency to infectious disease emergencies, and negative results in the right clinical context may prompt further investigation for a specific etiology.

SUMMARY

By having a working knowledge of emerging infectious disease and biothreat landscape, an emergency physician becomes a key component of the infectious disease emergency system.

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