Severe Febrile Respiratory Illnesses As a Cause of Mass Critical Care

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Febrile respiratory illnesses with respiratory failure are one of the most common reasons for admission to the intensive care unit. Most causes of febrile respiratory illness are bacterial and viral agents of community-acquired pneumonia. However, a small number of rare and highly contagious agents can initially present as febrile respiratory illnesses, which can lead to an epidemic that can greatly impact the health care system. This impact includes sustained mass critical care, with potential scarcity of critical resources (eg, positive-pressure ventilators), spread of disease to health care workers, sustained spread within the community, and extensive morbidity and mortality. The main agents of febrile respiratory illness that would lead to an epidemic include influenza, the coronavirus that causes severe acute respiratory syndrome, smallpox, viral hemorrhagic fever, plague, tularemia, and anthrax. Recognition of these agents occurs largely based on epidemiological clues, and management consists of antibiotics, antivirals, supportive care, and positive-pressure ventilation. Acute respiratory failure and acute respiratory distress syndrome occur with these agents, so a lung-protective (low tidal volume) ventilation strategy is indicated. Additional respiratory care measures, such as nebulized medications, bronchoscopy, humidified oxygen, and airway suctioning, potentiate aerosolization of the virus or bacteria and increase the risk of transmission to health care workers and patients. Thus, appropriate personal protective equipment, including an N95 mask or powered air-purifying respirator, is indicated. A basic understanding of the epidemiology, clinical findings, diagnosis, and treatment of these agents will provide a foundation for early isolation, evaluation, infection control, and public health involvement and response in cases of a febrile respiratory illness that causes respiratory failure. *Key words: acute respiratory distress syndrome, bioterrorism, febrile respiratory illness, infection control, respiratory failure.* [Respir Care 2008;53(1):40–53. © 2008 Daedalus Enterprises]

Introduction

Febrile respiratory illness (FRI) is a common reason for admission to an intensive care unit (ICU), and many cases develop into acute respiratory failure and acute respiratory distress syndrome (ARDS).[1,2] Most FRIs in patients admitted to the ICU are caused by community-acquired pneumonia, and up to 11% of these patients subsequently develop respiratory failure and ARDS.[3,4] However, other more rare infections, such as severe acute respiratory syndrome (SARS), plague, or a novel strain of influenza, can present as FRI, acute respiratory failure, and ARDS.[5–7] These rare causes can have a large impact on the health care and public health system due to their potential to create a mass casualty event. Therefore, early recognition of these rare infections is important for 2 reasons. First, early infection control and public health preparedness strategies can be implemented to reduce spread in both the public and health care arena, particularly in the early phases of disease, when patients are most contagious and likely to undergo aerosol-generating procedures by health care workers.[1,2,5,8–10] Second, public health and health care systems can implement mass casualty response plans that can prepare for the surge in patients with FRIs, acute respiratory failure, and ARDS. This paper will review the main infectious agents that can create a sustained mass casualty event that necessitates emergency mass critical care (EMCC), including the management of these patients and the basic infection-control measures that respiratory therapists will need during potentially higher-risk procedures.

Importance of Febrile Respiratory Illnesses

Although FRI is a common reason for admission to the ICU, early recognition and appropriate isolation of a patient with an FRI is important to reduce the likelihood of transmission within the ICU to health care workers, visitors, patients, and ultimately to the community. The etiologic list (Table 1) of FRIs is long, with many viral, bacterial, and fungal organisms likely. Both bacterial and viral causes of community-acquired pneumonia and subsequent respiratory failure compose the majority of cases.[3] However, a small number of rare agents have the potential to cause widespread epidemic and greatly impact the health care system (Table 2). These agents are highly contagious and include some of the Centers for Disease Control and Prevention (CDC) Category A agents of bioterrorism.[11] Many of these agents, such as pandemic influenza and plague, can spread quickly worldwide and create a situation of sustained mass casualty, extending medical resources and the health care system for weeks to months under EMCC.[12,13] This sustained EMCC will stretch crit-

Table 1. Potential Causes of an Acute Febrile Respiratory Illness with Respiratory Failure in an Immunocompetent Host

Bacterial Community-Acquired Pneumonia
Pneumococcus
Haemophilus influenzae
Moraxella catarrhalis
Community-associated methicillin-resistant *Staphylococcus aureus*
Mycoplasma
Other atypical agents
Viral Community-Acquired Pneumonia
Influenza
Respiratory syncytial virus
Adenovirus
Parainfluenza
Unusual Agents
Tularemia
Anthrax
Plague
Viral hemorrhagic fever
Varicella zoster virus
Hantavirus
Cryptococcus
Noninfectious Agents
Interstitial pneumonia
Eosinophilic pneumonia
Pulmonary embolism
Malignancy

Table 2. Naturally Occurring or Intentional Causes of a Febrile Respiratory Illness That Leads to a Sustained Mass Casualty Event

Influenza*
Viral hemorrhagic fevers*
SARS coronavirus*
Smallpox*
Plague*
Tularemia
Anthrax

*Contagious
SARS = severe acute respiratory syndrome

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ical care resources and the ability for self and community protection.[12,13] Since the potential scarcity of these critical care resources is greatest with these agents, a standard approach of early recognition and isolation of the FRI, followed by early and aggressive diagnostic testing, treatment, public health involvement, and response plan activation, is paramount.

Unfortunately, the exact etiology of an FRI that causes respiratory failure is often unknown at the time of admission to the ICU.[3] About half of FRIs with respiratory failure are diagnosed shortly after admission as bacterial community-acquired pneumonia, with a smaller number of cases determined to be viral when initial bacterial studies are negative.[3] The rare agents listed in Table 2 are more difficult to detect early in presentation, and detection often relies on particular epidemiological risk factors and early clinical suspicion. These epidemiological risk factors include contact with an animal vector, travel to an endemic area, a known laboratory-worker exposure, increasing number of cases in the community, or a known bioterrorism event. Therefore, even though these agents are uncommon, special recognition and intervention should begin at first presentation of an FRI to the health care system (Fig. 1). In most cases an etiology for the FRI can be determined quickly, and concern about a highly contagious, high-impact agent can disappear. However, if an etiology is not determined or if an epidemiological risk factor is identified (increasing number of cases of an FRI are detected within the community), a shift to advanced diagnostics, aggressive infection control, public health involvement, and, if indicated, early activation of critical care surge capacity plans could be initiated. Early protection and interventions with an FRI therefore can have a great impact if one of these rare, highly contagious agents does appear. Therefore, familiarity with the most common pathogens that cause FRIs and respiratory failure in an EMCC situation is imperative.

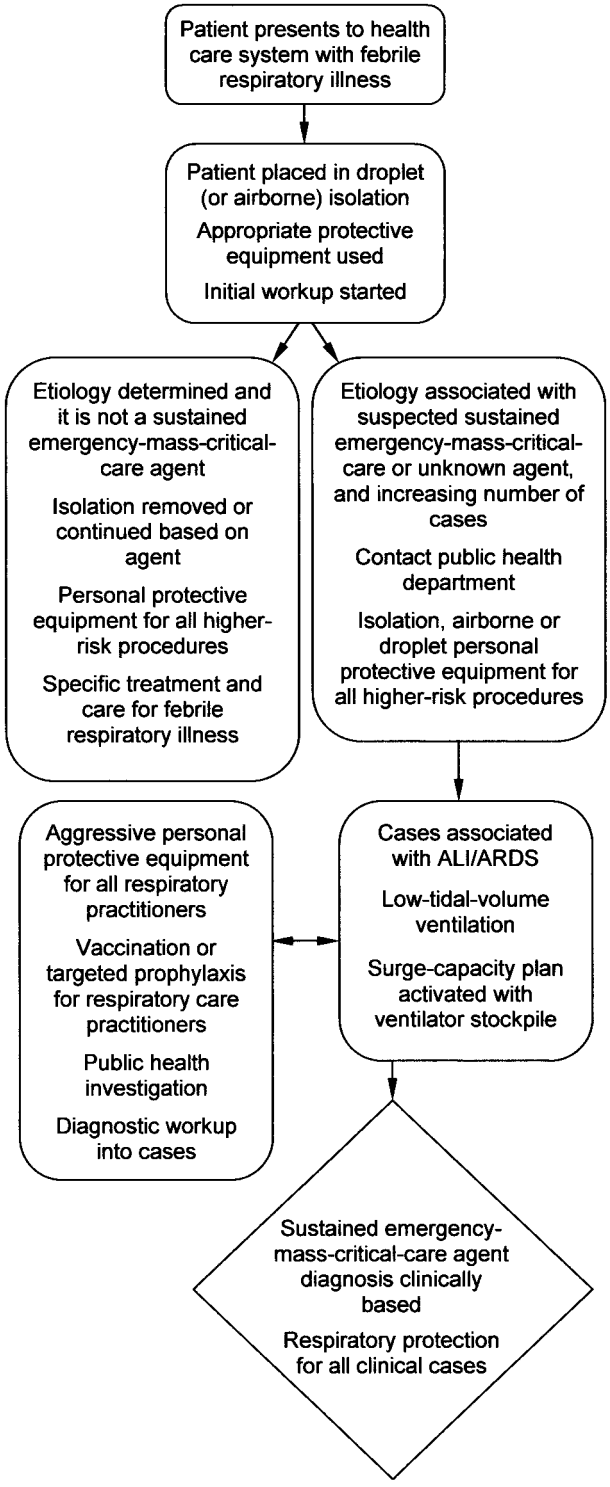

Fig. 1. Flow of patient care, infection control, and respiratory care practice in patients with febrile respiratory illness who present to a health care system. ALI = acute lung injury. ARDS = acute respiratory distress syndrome.

Febrile Respiratory Illnesses in the Setting of Sustained Emergency Mass Critical Care

Influenza

Influenza A or B can cause an acute respiratory illness, often during seasonal outbreaks.[14] Influenza A has 2 surface glycoproteins that determine subtype: a hemagglutinin and neuraminidase. Three major hemagglutinin subtypes (H1, H2, and H3) with 2 neuraminidase subtypes (N1 and N2) have been described in humans in seasonal epidemics, and a total of 16 HA subtypes and 9NA subtypes have been described in multiple species in nature.[14] Influenza B has less glycoprotein variability and is seen only in human disease and does not play a role in pandemics.[14] Both influenza A and B circulate yearly, with

slightly different strains developing each year due to genetic variation.[14] Though these strains vary yearly through antigenic drift, a large re-assortment, or antigenic shift, in the virus is more uncommon. This re-assortment occurs when the genome of one strain is mixed with another strain, leading to a novel subtype that has not circulated in the human population. Though a novel subtype is more likely to develop via re-assortment, antigenic drift can also lead to an important change that can cause a pandemic; this possibility highlights the worry about avian influenza infections in humans.[15] In addition to a novel subtype development, a pandemic requires little or no host (human) immunity, the ability of the novel subtype to cause substantial disease, and efficient contagiousness.[15] Thus, without population immunity and high contagiousness, a large number of cases would be seen heralding the onset of sustained mass casualty and the need for EMCC.[14]

Most cases of influenza are self-limiting infections with nonspecific symptoms such as fever, headache, myalgias, and malaise (an influenza-like illness).[14,16] However, during a pandemic with influenza A, many individuals are likely to develop a primary pneumonia.[14,16–19] After an influenza-like illness, the respiratory symptoms will progress, and respiratory failure with ARDS develops.[14,16–19] In seasonal epidemics, individuals at higher risk and with chronic pulmonary disorders traditionally develop respiratory failure, but with a novel subtype in a pandemic, healthy individuals with respiratory failure and ARDS will occur in increased numbers.

The recent outbreak of the highly pathogenic avian influenza H5N1 in humans illustrates the potential clinical picture in a pandemic. Most patients report contact with sick or dead poultry (although a few human-to-human cases of transmission have occurred) with the subsequent development of a fever, followed by a severe primary pneumonia, with respiratory failure and ARDS.[6,20–28] Respiratory failure with multiple organ damage is seen in over 60% of cases, and total mortality is over 60%.[29] Once admitted to the ICU with respiratory failure, the mortality exceeds 90%.[29] Although the current mortality of H5N1 appears to be higher than prior pandemics, the rapid development of pneumonia with respiratory failure in younger, healthy individuals illustrates the potential clinical picture in a pandemic.

Definitive diagnosis can be made via viral detection in an oropharyngeal aspirate, swab, or lower-respiratory-tract sample in a patient with appropriate clinical symptoms.[14] Viral subtyping is done via polymerase chain reaction in public health laboratories only. However, during a pandemic or seasonal epidemic, diagnosis can be made clinically with good reliability: a combination of fever, malaise, and cough had a 79% positive predictive value.[14,16,30] However, the use of a clinical diagnosis is limited to epidemiological data showing timely circulation within the community and thus is poorly accurate in ICU admissions when other etiologies may confound the diagnosis.[30] Rapid influenza viral diagnostic tests via immunofluorescence or enzyme immunoassay can provide rapid, reliable testing and can detect influenza A or B strains.[14] These tests are useful for rapid testing in a field or mass casualty setting, but their use depends on the influenza activity in the community.[31] During peak influenza season, rapid testing can be used to guide patient care or outbreak management. However, outside of influenza season or if influenza surveillance is unknown, rapid testing has a much lower sensitivity, and positive results must be viewed with caution.[31] Thus, confirmatory testing with culture or real-time polymerase chain reaction should be performed in these situations.[31] In addition, influenza viral shedding peaks at 48 hours of illness and declines thereafter, so polymerase chain reaction testing of a lower-respiratory-tract sample in a patient with respiratory failure and ARDS may be more beneficial.[14,16] Subtyping of a suspected case of influenza-related FRI with ARDS requires virus isolation that will be sent to a public health laboratory.

Neuraminidase inhibitors will be the treatment of choice during a pandemic.[28] Studies with the neuraminidase inhibitors involving seasonal influenza show a reduction in symptom time and viral shedding, and best effect is seen when the drug is started within 48 hours of symptom onset.[28] Treatment with neuraminidase inhibitors after 48 hours may provide some additional benefit but has not been fully studied.[28] With avian influenza (H5N1), higher viral levels and more sustained viral replication is seen, and in some cases H5N1 disease occurred after only 3 days of antiviral treatment.[32] Thus, with avian influenza (H5N1) the optimal duration of treatment is unknown. Viral resistance to neuraminidase inhibitors is low within the community for both seasonal and avian strains.[28] However, in animal models, higher doses of oseltamivir appear to be beneficial with certain clades of avian influenza A (H5N1), and in a few human cases, early treatment with standard doses led to oseltamivir resistance.[32] Therefore, neuraminidase dosing and duration of treatment will depend on local circulating clades, resistance patterns, and prior oseltamivir use.[32] Neuraminidase inhibitors will also be used for health care worker and community exposure prophylaxis.

The initial detection of a novel strain that signals the beginning of a pandemic is difficult. Influenza should be suspected during the winter epidemic season or if travel to an endemic area has occurred.[14,16] Avian influenza is suspected initially by the epidemiological link of contact with sick and dead birds. Therefore, the initial detection and determination of a novel strain will most likely be detected by subtyping in a public health laboratory, not by initial epidemiological risk factors. Transmission is primarily via droplets and contact with respiratory secretions, so pa-

Table 3. Infection Control and Respiratory Protection for Selected Agents of Febrile Respiratory Illnesses in a Sustained Mass Casualty Event Situation

Agent	Isolation	Baseline Protection	Protection in Higher-Risk Procedures
Influenza (novel strain)	Airborne and contact	N95 mask	N95 mask or respirator*
Viral hemorrhagic fever	Airborne and contact	N95 mask	N95 mask or respirator
Smallpox	Airborne and contact	N95 mask	N95 mask or respirator
SARS coronavirus	Droplet and contact	Surgical mask	N95 mask or respirator
Plague	Droplet and contact†	N95 mask	N95 mask or respirator
Tularemia	None	None	Surgical
Anthrax	None	None	Surgical

*Powered air-purifying respirator
†Isolation can be stopped after 48 h of appropriate antibacterial therapy.
SARS = severe acute respiratory syndrome

Table 4. Respiratory Care Procedures That Have a Higher Risk of Disease Transmission From Patients With Febrile Respiratory Illness

Nebulization of medication
Endotrachael intubation
Nasotracheal suctioning
Noninvasive positive-pressure ventilation
Bag-valve-mask ventilation
Bronchoscopy
Humidified oxygen delivery
Use of nonrebreather mask without expiratory filter

tients suspected of influenza infection should be placed in droplet isolation and health care workers should wear surgical masks, face shields, eye protection, gowns, and gloves as the appropriate personal protective equipment (PPE) (Table 3).[2,33,34] If a novel strain is detected via laboratory testing, health care workers should wear an N95 mask, and the patient should be placed in airborne isolation instead, until the mechanism of transmission is further understood.[35] Based on the SARS experience, higher-risk procedures that generate aerosols (Table 4) may require the use of an N95 mask or a powered air-purifying respirator, because of the potential to facilitate disease spread.[2,5,7,36] Finally, any suspected case of a novel strain of influenza or a surge in cases of an FRI with respiratory failure should prompt an urgent notification to local public health officials so a novel subtype can be verified and community measures to reduce spread can be instituted

Severe Acute Respiratory Syndrome

SARS is caused by a novel coronavirus that was first detected in 2003.[5,7] This novel virus appears to have evolved from a horseshoe bat coronavirus and spread to humans after investigations showed remarkable genetic similarity between the bat and human strains. Thousands of cases occurred worldwide in the initial epidemic in 2003, but the epidemic abated and new cases have not been reported since. The clinical presentation is characterized by fever, chills, rigors, malaise, nausea, and shortness of breath initially, with the later development of respiratory failure.[5,7,37] The symptoms occurred on average 7 days after contact. Pneumonia appeared to develop approximately 8 days after onset of fever, and 45% of patients developed hypoxemia. About 20% of patients went on to develop severe lung injury and ARDS that required mechanical ventilation.[7,37,38] Development of ARDS from onset of fever is bimodal, with peaks at 11 and 20 days. The global fatality rate was 11%, and most of the deaths were in patients over age 65.[7,37,38] No deaths were reported in children.[7,37,38]

Diagnosis includes an influenza-like illness with severe pneumonia in the presence of the epidemic or laboratory exposure with viral detection via real-time polymerase chain reaction with respiratory samples.[5,7,10,37,38] Only the CDC can perform public health testing currently. Treatment is largely supportive, but steroids were used in some cases after the development of ARDS.[5,7,10,37,38] However, experience with steroid use was very limited, and in some cases may have caused harm, so benefit remains uncertain.

Initial cases in 2003 were difficult to identify, which resulted in extensive spread to health care workers. Transmission is via the droplet route, although many cases suggest that airborne and contact routes also occur, and outbreak analysis has not ruled out oral-fecal spread as well (see Table 3).[2,39] Spread to health care workers who wore appropriate PPE suggested airborne transmission in some circumstances, particularly when the spread occurred during aerosol-generating procedures such as cardiopulmonary resuscitation, intubation, medication nebulization, and noninvasive positive-pressure ventilation.[5,8,39–41] However, the spread of SARS with higher-risk procedures was largely experienced in Canada and not reproduced in the Asian cases, which suggests that differences in PPE use or procedure administration play the largest role in disease

spread. Regardless, the experience with SARS, particularly among health care workers, recommends an approach to care that requires early isolation and enhanced PPE when engaging in certain higher-risk procedures (see Table 4).[2,35,39,42] The epidemic waned within a few months, so detection based on clinical grounds would require a high level of suspicion in either the context of a known laboratory exposure or a new confirmed SARS outbreak with epidemiological risk. Therefore, any consideration of SARS or another potential virus should promptly be reported to hospital infection control and the public health officials.[35]

Viral Hemorrhagic Fevers

The hemorrhagic fever viruses include a number of geographically distributed viruses found worldwide, including the Ebola and Marburg viruses, Rift Valley fever, Crimean Congo hemorrhagic fever, Lassa fever, yellow fever, and dengue fever. The Ebola and Marburg viruses are in the family *Filoviridae*.[43] Although any of the many viral hemorrhagic fevers can cause an FRI, Marburg and Ebola virus serve as a classic template for viral hemorrhagic fevers and will be largely discussed here.[44–46]

Marburg virus has a single species, whereas Ebola has 4 different species, which vary in virulence in humans.[44–46] Transmission appears to occur through contact with nonhuman primates and infected individuals. Settings for transmission have included vaccine workers handling primate products, nonhuman primate food consumption, nosocomial transmission, and laboratory worker exposure.[47–50] The use of viral hemorrhagic fever in bioterrorism has also been postulated, largely based on its high contagiousness in aerosolized primate models.[49] The exact reservoir for the virus was initially thought to be with wild primates, but recently bats have been labeled as the reservoir, passing the infection onto nonhuman primates in the wild.[49]

The clinical manifestations of both Marburg and Ebola virus are similar in presentation and pathophysiology, and mortality is the only major difference between them. The initial incubation period after exposure to the virus is 5–7 days, and clinical disease begins with the onset of fever, chills, malaise, severe headache, nausea, vomiting, diarrhea, and abdominal pain.[49,51–53] Disease onset is abrupt, and over the next few days symptoms worsen and include prostration, stupor, and hypotension. Shortly thereafter, impaired coagulation occurs, with increased conjunctival and soft-tissue bleeding.[43,49,53] In some cases more massive hemorrhage can occur in the gastrointestinal and urinary tract, and in rare instances alveolar hemorrhage can occur.[49,51–53] The onset of maculopapular rash on the arms and trunk also appears classic and may be a very distinctive sign. Along with the bleeding and hypotension, multiple organ failure occurs, eventually leading to death.[43,49,53] Reports of outbreaks and cases have largely occurred in developing countries, where critical care resources are more limited, so experience with mechanical ventilation and the development of ARDS is not well documented. Case fatality rates reached 80–90% in the recent outbreak of Marburg virus in Angola, but Ebola case fatality appears to be lower, at 50%.[43–5,49,53]

The diagnosis of viral hemorrhagic fever becomes extremely important in order to initiate supportive care before the onset of shock, to alert and involve the public health department, and to institute infection-control measures. However, diagnosis is difficult outside of the endemic area. Viral hemorrhagic fever should be suspected in cases of an exposed laboratory worker, an acutely ill traveler from an endemic area (ie, central Africa), or in the presence of some classic clinical findings with an increasing number of cases in the community, which suggests a bioterror attack.[49,54] Outside of travel or laboratory exposure, the presence of a high fever, malaise and joint pain, conjunctival bleeding and bruising, confusion, and progression to shock and multiple organ failure should raise suspicion of a viral hemorrhagic fever, particularly if multiple cases are presenting in the community.[55,56] Laboratory diagnosis includes antigen testing via enzyme-linked immunosorbent assay or viral isolation via culture, but these tests are currently performed only by the CDC.[54] Because no specific therapy is available, patient management includes supportive care, including a lung-protective strategy with low-tidal-volume (low-V_T) ventilation if ARDS appears as part of the disease course.[49,57] In a few cases in an outbreak in 1995 in the Democratic Republic of Congo (formerly Zaire), whole blood with immunoglobin G antibodies against Ebola may have improved outcome, although analysis showed these patients were likely to survive anyway.[58]

Although transmission appears to spread via the droplet route, airborne precautions are recommended, with respiratory protection with an N95 mask or air-purifying respirator and placement of the patient in a respiratory isolation room.[49,57] Equipment should be dedicated to that individual, and all higher-risk procedures should be done with adequate, full PPE (see Table 4).[49,57] Any suspected case of viral hemorrhagic fever should immediately involve the public health officials and infection-control department, as public health interventions and outbreak investigation will be paramount to reduce spread of disease within the community and to investigate any potential bioterror attack.[55,56] If exposure to a health care worker occurs, there is no specific post-exposure prophylaxis, and infection control and occupational health should be involved with potential quarantine measures for exposed individuals.

Smallpox

Variola virus is the causative agent of smallpox and is a member of the *Poxviridae* family.[59] Smallpox was eradicated worldwide in 1977 but now has regained interest as a potential bioterrorism agent.[60,61] Smallpox was endemic worldwide, and at one point accounted for over 10% of all deaths worldwide, until the last endemic case in Somalia in 1977. It occurs in 2 forms: variola major and variola minor.[59] Variola major is the most common form of smallpox, has more severe disease, with an extensive rash and fever, and carries a higher mortality (around 20% in the unvaccinated).[59] Variola minor is less common and severe, with mortality historically under 1%.[59] Variola major has a very similar genetic sequence to variola minor; gene expression differences probably cause the different mortality between major and minor. Smallpox is very contagious; approximately half of all unvaccinated household contacts contract the disease. However, after worldwide eradication in 1977, routine vaccination for smallpox ceased worldwide.[62] But because of an increasing unvaccinated population, along with the disease's contagiousness and ability to be transmitted via aerosol, smallpox is a CDC Category A bioterrorism agent. Only 2 stockpiles of the virus remain (at the CDC and Russian State Research Center) for continued research.[59]

Smallpox infection occurs when the viral particles enter the respiratory tract, replicate locally, and then are carried to regional lymph nodes.[59,61,62] Subsequent viremia occurs, with spread to lymphoid organs, followed by further viral amplification and progression of symptoms. Variola major occurs in 5 main clinical categories: ordinary, modified, flat, hemorrhagic, and variola sine eruptione.[59] Ordinary type infection accounted for more than 70% of cases.[59,61,62] After an incubation period of 10–14 days, disease onset (pre-eruptive phase) occurs, with high fever, severe headache, and malaise.[59,61,62] The pre-eruptive phase can last 2–4 days and is followed by the eruptive phase, which is characterized by rash. The lesions first appear as small erythematous macules on the mucous membranes, tongue, and face (herald spots). Spread then occurs in a centrifugal fashion, with macules evolving into papules, then vesicules, and finally the classic pustules (pox) by day 5–7 of the rash. Fever usually resolves during the eruptive phase but may occur after the pustules develop.[59,61,62] Crusting and healing begin by day 14 of the rash. The modified type of variola major is similar to the ordinary except for a more rapid but less severe rash, as this type was common in vaccinated individuals.[59,61,62] The flat type had pustules that remained flat and confluent, and often occurred in children. The hemorrhagic type was rare but very severe, with the lesions and mucous membranes becoming hemorrhagic.[59,61,62] This type was more common in pregnant women and rapidly led to multiple organ failure within a few days. Variola sine eruptione would have a fever but no rash, and this was often found in previously vaccinated individuals as well.[59,61,62]

Diagnosis is largely clinical, with the acute onset of fever followed by the characteristic rash of deep-seated vesicles or pustules. For laboratory diagnosis, virus isolation from a skin lesion with real-time polymerase chain reaction confirmation is used, and performed only at the CDC or World Health Organization laboratory.[61] Treatment is largely supportive, but there is some evidence that cidofivir has activity in animal models.[63,64] Vaccination early in disease may also reduce the severity of illness and is the mainstay of reducing spread and controlling disease in the community.[61] Mortality for ordinary type was around 20% from multiple organ failure and hypotension. The flat and hemorrhagic types had a higher mortality. The modified and sine eruptione types had a much lower mortality.[62,63] Complications include secondary bacterial skin infections and pneumonia, along with encephalitis, orchitis, and extensive scarring of the skin and cornea.[62,63]

Respiratory management in the ICU includes support with positive-pressure ventilation in cases with respiratory failure associated with ARDS or a lobar, secondary bacterial infection in the face of multiple organ failure.[62] Spread is through contact with infected lesions or respiratory secretions, and thus full PPE, including gown, gloves, and face shield are required.[65] CDC guidelines recommend airborne isolation, with use of an N95 mask or a powered air-purifying respirator for respiratory protection, and all health care workers handling any smallpox patient must receive the vaccination.[66] Any suspected case of smallpox should immediately involve public health officials.[65]

Plague

Yersinia pestis is the etiologic agent of plague and has caused a number of pandemics throughout human history.[67] Plague is a zoonosis that primarily affects rodents; humans and other animals (eg, domestic cats) are accidental hosts.[68] The natural ecosystem of *Y. pestis* depends largely on the flea and rodent interaction, with seasonal variability noted based on environmental conditions.[67,69] Infected fleas bite their rodent hosts, inoculating the rodent. Mortality in these animals remains lower than other nonrodent mammals, and disease is passed from infected rodent to flea and the life cycle continues. Transmission to humans occurs via rodent flea bites, infected animal scratches or bites, exposure to infected humans, and bioterrorism.[67,69,70] Transmission via infected flea bite is the most common mode, with squirrel, rabbit, domestic cats, and prairie dogs being the most common animals of transmission.[67,69] Large rodent or other animal die-offs, particularly in more susceptible species, may herald a large epidemic in nature.[67,69] Plague is found worldwide, and in

the United States endemic disease is found largely in the western states.[67,69] The most recent outbreaks, in 1992, occurred in Africa, South America, and Asia.

Three recognized clinical syndromes are associated with plague: bubonic plague (80–90% of cases), septicemic plague (10% of cases), and pneumonic plague (very rare).[69–71] After an incubation of 2–7 days, clinical symptoms usually occur and differ depending on clinical syndromes. In bubonic plague, a sudden onset of fevers, chills, and headache is followed by intense pain and swelling in the regional lymph nodes proximal to the site of the bite or scratch.[69] This lymph node, or bubo, is characterized by intense tenderness with erythema and edema, but without fluctuation. Without treatment, disease disseminates, leading to complications such as pneumonia, meningitis, sepsis, and multiple organ failure. The development of a secondary pneumonia is extremely concerning, because these patients are highly contagious.[69]

Septicemic plague involves acute fever followed by sepsis, without the presence of a bubo.[68,69,72] Gastrointestinal symptoms such as nausea, vomiting, and diarrhea also complicate septicemic plague. Rapid sepsis, disseminated intravascular coagulation, and multiple organ failure develop quickly after the inoculating flea bite.[68,69,72]

In pneumonic plague, most cases are secondary to bubonic or septicemic plague, but a primary pneumonic plague could occur after exposure to infected humans, animals, or aerosols in an intentional bioterror attack.[69,71,73,74] Because of the high contagiousness of plague, disease can spread rapidly, with primary pneumonia, as seen with past outbreaks in human history, subsequently creating a sustained pandemic.[69,71] Initial cases in primary pneumonic plague have a very short incubation period of hours to a few days, followed by sudden onset of fever, cough, rapid onset of respiratory failure and ARDS, and death.[69–71]

Diagnosis is primarily via culture of sputum or blood, as *Y. pestis* grows well on most laboratory media.[69,73] Serology and rapid diagnostic testing via enzyme-linked immunosorbent assay or polymerase chain reaction is also available, but is used primarily in field testing.[69,73] Treatment has been considered streptomycin, but based on its limited availability, gentamicin or doxycycline is preferred.[69,70,73,75] Chloramphenicol is preferred for cases of meningitis because of its ability to cross the blood-brain barrier.[70]

Pneumonic plague and septicemic plague in the ICU will have multiple organ failure with ARDS, so management should include a protective lung strategy with low-tidal-volume ventilation and appropriate supportive care.[69,70,76] Because of the high rate of transmission of plague via aerosols, all patients should be in strict airborne isolation until at least 48 hours of antibiotics have been given.[70] Appropriate PPE, including an N95 mask or air-purifying respirator, should be worn, and any exposure by a health care worker should receive prophylaxis with doxycycline, chloramphenicol, or trimethoprim-sulfamethoxazole.[70]

Tularemia

Tularemia is caused by the Gram-negative bacterium *Francisella tularensis* and is a zoonotic disease; humans are accidental hosts.[77–79] *F. tularensis* is found throughout the northern hemisphere and in a wide variety of wild and domesticated species.[77,80,81] The organism persists in nature because it is passed transovarially in ticks, with disease coming after bites from infected vectors (ticks, flies, mosquitoes).[77–79] Susceptibility varies by species; rabbits and rodents have particularly severe disease, with near 100% mortality. Human infections occur via vector contact (ticks and flies), the handling of infected animals, improperly prepared animal meat, animal scratches and bites, the drinking of contaminated water, or aerosolization of the organism from the environment or in bioterrorism.[77–81] However, human-to-human transmission does not occur, largely because the organism is intracellular during infection and thus harder to spread from person to person.[77,80,81]

Approximately 6 distinct clinical syndromes occur with tularemia: ulceroglandular, glandular, typhoidal, pneumonic, oropharyngeal, and oculoglandular.[77,79,82] Ulceroglandular disease accounts for approximately 60–70% of disease. Abrupt onset of fever, chills, headache, and malaise occurs after an incubation period of 2–10 days.[77,79,82] Most patients will have a single papuloulcerative lesion with a central eschar and associated tender lymphadenopathy.[77,79,82] In glandular disease, enlargement of lymph nodes occurs without the characteristic lesion (about 15% of cases). Pneumonic tularemia occurs after primary inhalation or hematogenous spread from typhoidal tularemia, and this is expected to be the main clinical presentation in a bioterrorism event with tularemia.[78,79,83,84] The incubation period tends to be shorter in these cases, with the rapid onset of pneumonia. Radiograph shows patchy infiltrates bilaterally, lobar disease, and hilar adenopathy.[79,83,84] Pleural effusions and a miliary pattern can also occur, although this is less common.[79,83,84] Respiratory failure and ARDS develop quickly. Typhoidal tularemia is rare and can occur with or without pneumonia, as patients present with a febrile illness followed by sepsis, but without the glandular disease.[79] Oropharyngeal tularemia occurs rarely, when undercooked infected meat or water is ingested, and is associated with fever, pharyngitis, and cervical lymphadenopathy.[79] Oculoglandular tularemia occurs with direct inoculation from contaminated fingers or accidental exposure. Besides conjunctival swelling and erythema, regional lymphadenopathy may be present.[79]

F. tularensis is very difficult to grow on culture media (requires cysteine), and since it is largely an intracellular organism, diagnosis is difficult.[85] Clinical suspicion must be high, particularly if there are risk factors of vector exposure, animal exposure, or multiple community cases, which suggests aerosolization. Therefore, serology via enzyme-linked immunosorbent assay or histologic examination that shows Gram-negative intracellular organisms is the most likely method.[79,86] If serology is performed, a single elevated titer may not be specific, and thus acute and convalescent titers are more predictive.[87,88] For meningitis, chloramphenicol is preferred. The overall mortality of tularemia is around 4%, but is thought to be higher with aerosolized disease that causes pneumonia or typhoidal tularemia.[79]

Particular ICU management of tularemia includes supportive care and low-V_T ventilation for ARDS.[76] Human-to-human transmission does not occur, so once the diagnosis is confirmed, respiratory isolation can be lifted.[78] Tularemia is a zoonosis, so prevention is largely vector and exposure avoidance.[79,82] Prophylaxis is not needed for human exposures but is indicated for aerosol exposure in an outbreak or bioterrorism event, as well as in a laboratory worker exposure.[78] Reporting of tularemia to public health officials varies across North America, but pneumonic or typhoidal cases, particularly if thought to be secondary to a bioterrorism event, should be reported.

Anthrax

Anthrax is caused by *Bacillus anthracis*, a sporulating Gram-positive rod.[89–91] There are 3 distinct stages to its ecology, including a soil stage, animal infection, and human infection.[89,90] Anthrax is part of the normal soil flora, where local multiplication occurs if soil conditions are right. Otherwise, anthrax will persist for long periods of time in a spore form, resistant to decontamination and environmental influences. Disease spreads to herbivores, such as cattle, as they come into contact with highly infectious soil through grazing.[89,90] Human disease largely occurs through contact with animal products such as animal skins, where the bacillus form converts back to the spore form. Human inoculation of spores occurs through inhalation or direct transmission through skin, where spores germinate to the bacillus or vegetative form.[89,90] In 2001, however, 22 cases of anthrax occurred in the United States from an act of bioterrorism through the postal system, which placed anthrax on the forefront of an FRI in a bioterrorism incident.[92,93] Outside of that event, anthrax remains relatively rare in the United States; most endemic and epizootic cases occur in the Middle East.[78] Most cases in the United States occur through handling of animal products, such as the 2006 cases associated with African animal-hide drum skin.[94,95] The threat of anthrax still remains as a bioterrorism and zoonotic agent.

Disease occurs when the spore form is introduced subcutaneously or via inhalation, becomes the vegetative (bacillus) form, and starts replication.[89,90] Endotoxin secretion, along with a thick capsule that avoids phagocytosis, leads to local spread, edema, hemorrhage, and tissue necrosis.[89,90,96] In the inhalational form, small (2–5 μm) spores are deposited in the distal alveoli, where they undergo phagocytosis and are transported to the mediastinal lymph nodes. In the lymph nodes, they multiply and begin to cause disease.[89,90,96] The anthrax capsule along with an edema factor toxin and lethal factor toxin act in concert to drive disease.[89,90,96] In overwhelming disseminated anthrax these factors will ultimately lead to multiple organ failure and death.

Three clinical disease syndromes occur with anthrax: cutaneous, gastrointestinal, and inhalational.[89,90,97,98] Cutaneous anthrax is the most common form worldwide and follows an incubation period of 7–14 days after inoculation of spores into the subcutaneous space.[91] This is followed by a small, painless papule that can be pruritic. This papule quickly enlarges and develops a central vesicle, followed by erosion into a painless black eschar.[91] Edema surrounds the tissues and regional lymphadenopathy also may occur, along with systemic symptoms of fever and malaise.[91] The hands, arms, face, and neck are the most common areas affected.[91] With inhalational anthrax, the spores that reach the distal airways are brought into the mediastinal lymph nodes, where replication occurs, followed by onset of disease.[90,94,95,98] The incubation period averages 1–7 days, followed by clinical symptoms of a nonspecific febrile illness, which often mimics influenza. However, within 24 hours, disease rapidly progresses, with the development of respiratory failure, hemorrhagic mediastinitis, necrotizing pneumonia, shock, multiple organ failure, and death.[90,94,95,98] As with plague and tularemia, the development of shock and multiple organ failure can occur rapidly. Gastrointestinal anthrax is rare and occurs after the consumption of undercooked meat from an infected animal, usually in family clusters.[97] Bowel edema, followed by mesenteric lymphadenitis and necrosis occur, with rapid progression to shock and death.[97] The mortality of cutaneous anthrax remains low, at less than 1% in treated patients (20% in untreated), whereas inhalational anthrax can carry a mortality of 89%.[89,90] The inhalational cases from 2001 in the United States had a lower mortality of 45%.

The diagnosis of anthrax is best performed via culture of the blood, sputum, pleural fluid, cerebrospinal fluid, or skin.[90,91] Clinicians should notify laboratory personnel of suspected anthrax, since spore formation during culture can occur, leading to spread to laboratory workers if not properly handled.[90,91] Additionally, any suspected case of

anthrax should involve the public health laboratories for confirmation and strain typing. Polymerase chain reaction and rapid enzyme-linked immunosorbent assay exist and have good sensitivity and specificity.[90,91,99–101] Treatment includes ciprofloxacin, doxycycline, and, if susceptible, penicillin.[90,91] The additional use of rifampin, clindamycin, or vancomycin in combination with ciprofloxacin occurred in the 2001 bioterrorism attacks, but penicillin was not used, because of resistance.[90,91,94,98] Appropriate pleural-space drainage or the use of a central nervous ventricular shunt may also be used in individual cases.[90,91,94,98]

Management of anthrax in the ICU in the 2001 attacks occurred with inhalational cases only.[90,94,98] Respiratory failure, along with shock and multiple organ failure, occurred. Thus, low-V_T ventilation would be beneficial, and in some cases, corticosteroids were used to reduce edema and hemorrhage.[76] Anthrax is not contagious, as the vegetative bacillus form of disease exists during clinical infection.[90,94,98] Contact with infected animals and animal products increases the likelihood of disease spread, so limiting contact or wearing the appropriate PPE, particularly in endemic areas, is indicated. A live virus vaccine, which is toxigenic and uncapsulated, has been used in veterinary medicine to control disease in animals, but use in humans has been more limited because of frequent dosing, adverse effects, and efficacy.[102] Its use is currently reserved for military personnel. Exposure to aerosolized spores requires prophylaxis with either ciprofloxacin or doxycycline in adults, and amoxicillin as a second-line therapy in children and pregnant women.[89]

Overlying Features and Approach to Treatment

Basic Respiratory Care and Protection

The management of critically ill patients with FRI and respiratory failure in a mass casualty setting will vary depending on the agent, severity of pneumonia and respiratory failure, and the use of antibiotics. However, many of these patients, regardless of etiology, will have similar features that will allow for uniform care and preparedness.

First, all agents that can cause an FRI in a mass casualty setting will present with respiratory distress and respiratory failure. Most of the cases will have a primary pneumonia or a secondary process that leads ultimately to acute lung injury and ARDS. Therefore, respiratory care measures used in ARDS can be uniformly applied. Paramount is the use of a lung-protective ventilation strategy.[76] Low-V_T ventilation, based on the ARDS Network study,[103] should be used in all causes, because it has been proven to lower mortality in patients with ARDS. Initial V_T of 6 mL/kg ideal body weight should be employed and lowered if the plateau pressure remains elevated.[3,76,104] Higher positive end-expiratory pressure should also be employed to limit atelectasis and barotrauma, although no mortality benefit has been proven.[76,104] Other maneuvers or modalities, including prone positioning and high-frequency oscillatory ventilation, have never been proven to reduce mortality, and in the setting of a surge of patients, these maneuvers involve extensive staff time and should not be routinely employed.[76] Therefore, delivering lung-protective ventilation will require a positive-pressure ventilator that can perform and monitor low-V_T ventilation, increased positive end-expiratory pressure, and variable airway compliance.[12,13,105]

The role of noninvasive positive-pressure ventilation (NPPV) in an FRI with hypoxemic respiratory failure and ARDS in a mass casualty setting is more complicated. In heterogeneous patient populations with acute hypoxemic respiratory failure, NPPV has been shown to reduce the likelihood of endotracheal intubation (57%), ICU stay, and, in some patient populations (cardiogenic pulmonary edema, obstructive lung disease), mortality.[106] In regards to ARDS as the cause for acute hypoxemic respiratory failure, a recent study at experienced NPPV centers showed that early application of NPPV led to improvement in gas exchange, avoidance of intubation, and less ventilator-associated pneumonia.[107] However, intubation remained high in patients when illness was more severe (Simplified Acute Physiology Score II > 35) or hypoxemia did not improve after 1 hour (ratio of P_{aO_2} to fraction of inspired oxygen [F_{IO_2}] < 175 mm Hg), which suggests that NPPV is a useful first-line therapy in early ARDS in less severe patients who respond quickly.[107]

With the SARS experience in Canada, NPPV was also associated with an increased risk of disease transmission. That experience was based largely on case studies and was not reported with SARS cases in Asia. Thus, the likelihood of increased disease transmission with other agents of FRI is less clear. A recent model of NPPV showed that air and particle dispersion occurred to 0.25 m with 10 cm H_2O of inspiratory pressure and a nasal leak.[108] Dispersion increased to 0.40 m with elimination of the nasal leak, and increased to 0.48 m with an inspiratory pressure of 18 cm H_2O.[108] The highest dispersion occurred lateral and horizontal to the median sagittal plane of the mask-face seal. Thus, substantial exposure to exhaled particles appears to occur within a 0.5 m radius of a patient receiving NPPV.[108] In summary, the use of NPPV with a patient who has an FRI and ARDS remains controversial; there may be some benefit possible in less severe, early ARDS cases. NPPV use may also carry a potential increase in disease transmission within a 0.5 m radius of the patient.

Other adjuvant therapy for an FRI with ARDS has been tried as well without consistent success. Steroids and other anti-inflammatory agents have been used in influenza, avian influenza, anthrax, and viral hemorrhagic fever.[20,28,36,41,71,92,98] However, this experience

has been limited to case reports only and has not been used routinely, and in some cases may be harmful. Other agents such as immunoglobulin therapy and aerosolized antibiotics have also been employed on a case report basis, but would be difficult to administer in a mass casualty setting.

In addition to respiratory distress and ARDS, these agents will often lead to multiple organ failure and hypotension, so supportive care will also be employed. Resuscitation with intravenous fluids, vasopressor therapy, and renal replacement therapy will be employed as indicated in these patients, and thus impact respiratory care.[2,12,13,105] Further management with higher-risk procedures (see Table 4) will also occur, and thus appropriate PPE should be used if the procedure is required.

Respiratory Infection Control

Since the etiology of a febrile respiratory illness is largely unknown upon admission to the ICU, isolation of the patient should occur immediately until further studies are performed (see Fig. 1).[3,4] Many emerging infections that cause FRI may not be isolated until later in the outbreak, so early isolation is encouraged for all FRIs.[3,5,7] These patients will additionally undergo potentially higher-risk aerosolizing procedures (see Table 4) that will increase the likelihood of disease transmission, putting both health care workers and other patients at risk of acquiring disease, as experienced during the SARS epidemic.[2,5,36] Therefore, a standardized approach to these patients in a mass casualty setting is imperative.

Figure 1 outlines an approach to early isolation, testing, and involvement of institutional infection control, infectious diseases, and public health in cases of an FRI with respiratory failure admitted to the ICU in a mass casualty setting. Initially, the first cases will present to the health care system without an obvious epidemiological link. Thus, all cases of an FRI with respiratory failure should immediately be isolated upon arrival. This practice should occur at all times, and once admitted the patient should subsequently undergo initial diagnostic testing, including pretreatment Gram-stain, respiratory culture, and urine antigen testing for *Legionella*. If an etiologic agent is identified on initial screening and clinical findings (ie, Gram-positive diplococci with a lobar pneumonia on radiograph), targeted treatment and ICU admission is performed. Further isolation of the patient can be discontinued at this point, depending on the identified organism. However, if an agent is not easily identified or if there are epidemiological clues that suggest a highly contagious agent of public health concern (see Table 2), the patient should remain in isolation and further diagnostic testing should be performed. Isolation should be based on specific epidemiological clues.[35] If the agent is suspected to be of public health concern (see Table 2), hospital infection control, infectious diseases, microbiology, and the public health officials should be notified immediately. In a case of public health concern, diagnostic measures, including bronchoscopy, should be performed in order to determine a diagnosis. Although bronchoscopy generates aerosols and can increase transmission risk, it should not be avoided in these cases, because etiology is important from a public health perspective, and transmission risk is low when the appropriate PPE is used. Bronchoscopy may be preferred for 2 reasons: (1) detection of an agent may be difficult if antibiotics have been given or in later stages of disease, or (2) isolation of a virus from a nasopharyngeal swab or aspirate is highest early in disease course, but by the time the patient has developed disease in the lower respiratory tract with respiratory failure, a lower respiratory tract sample may provide the highest yield. Certain testing, such as for smallpox and Ebola virus, is performed by the CDC, so all specimens should be collected and tested in conjunction with a public health laboratory. Patient isolation should remain until a diagnosis is established or the patient improves, remaining afebrile for at least 48 hours. Any change in isolation status should involve the institution's infection-control and infectious-disease specialist.

Once disease progresses within the community and multiple cases have been established, patient isolation can occur on admission in patients with an FRI and clinical findings consistent with the disease syndrome. Testing can be more limited, with diagnosis made clinically, and this may reduce the number of higher-risk procedures. Institutional infection-control, infectious-disease specialists, microbiology, and public health will be involved closely in creating a case definition and managing containment. Once the health care system has reached a sustained EMCC, testing will become difficult because of limited staff and resources, so isolation and ICU management will occur based on clinical grounds.

Finally, aerosol-generating procedures are most common in ICU patients with an FRI and respiratory failure, and health care workers are thus at high risk of exposure to these pathogens.[2,5,36] Most cases of transmission during aerosol-generating procedures, such as cardiopulmonary resuscitation and bag-valve-mask ventilation, are based largely on epidemiologic and case studies, and direct studies are lacking.[2,5,36] Additionally, transmission during some higher-risk procedures, such as high-flow oxygen and medication nebulization, is based on infectious potential and has not been documented with these agents. Regardless, appropriate PPE should be worn by respiratory therapists at all times, and, if worn properly, disease transmission is lower-risk and thus these procedures can be performed. In fact, they are crucial to the diagnosis in many cases of FRI with respiratory failure. Most cases during the SARS and avian influenza epidemic appeared to have occurred when

health care workers did not wear the appropriate PPE, which appears to be the largest risk factor for transmission to the health care worker.[2,5,36]

Summary

The cause of most FRIs with respiratory failure admitted to the ICU is either a bacterial or viral agent of community-acquired pneumonia. However, a small and rare number of highly contagious agents can present as an FRI with respiratory failure: influenza, SARS, smallpox, viral hemorrhagic fevers, plague, tularemia, and anthrax. These agents have a high likelihood of developing into a pandemic that will strain the health care system either under naturally occurring outbreaks or from bioterrorism. Thus, early recognition, isolation, and management become paramount to contain disease, provide adequate patient care, and prepare for sustained EMCC. Most of these agents are highly contagious (with the exception of anthrax and tularemia), and require all practitioners to wear appropriate PPE. Management in the ICU includes antibiotics, antivirals, and supportive care, as well as low-V_T positive-pressure ventilation, given the development of ARDS with all these agents. The additional use of protective equipment for higher-risk procedures is also indicated with all of these agents. In order to provide management and disease containment in EMCC, a comprehensive approach of early isolation and detection, to a lung-protective ventilation strategy, to activation of surge capacity plans, is required.

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Discussion

Hanley: In 1976 or '77 I was a medical student in Houston and remember getting vaccinated for swine flu influenza. It was going to be the next major pandemic and we were all going to die from it. I don't know whether it was the vaccination that was successful, but it seemed like that pandemic never occurred. How did that influenza virus differ from bird flu and are there lessons that we can take from that which might help us?

Sandrock: The swine flu virus was different from the bird flu strains in that the 1976 strain was an H1N1, likely leading to some herd immunity. There was an aggressive vaccination campaign, but there were a lot of complaints about the aggressive policy, and many cases of Guillain-Barré syndrome ensued. The difference with the bird flu is, genetically, it's such a different virus, with its hemagglutinin from a much different category. So,

for example, the swine flu—as all of our human flus—is very good at replicating in our oropharynx and our nares and was an H1 subtype. That is why we get infected if someone sneezes at us and we get a droplet in our mouth; the swine flu was one of these strains.

If you were to take avian influenza, it actually doesn't replicate very well in our oropharynx, but does great with type 2 pneumocytes in our alveoli. So I think it changes how this disease presents and how it spreads. I think this was—it just happened to be a less severe pandemic, and if you follow them, the 1918 pandemic was the most severe, the 1957 actually was less severe, the 1968 even less severe than that, then 1976, the least severe. Most authorities talk about herd immunity to explain this.

Now when you look at the vaccination, just so you know, people praise the vaccination as stemming the tide of this pandemic, but there were many issues when President Ford created that sudden policy. Interestingly enough, many of you have heard of getting Guillain-Barré from the influenza vaccine and developing respiratory failure. Almost all of that data come from that swine flu vaccine; it wasn't a very pure vaccine, and they gave it out in mass quantities, and most of that data came from there.[1] So that was the negative side of that aggressive campaign as well. There were 2 sides to it.

1. Gaydos JC, Franklin TH, Hodder RA, Russell PK. Swine influenza A outbreak, Fort Dix. New Jersey Emerg Infect Dis 2006; 12(1):23–29.

Rubinson: Legionella, which we did not know was Legionella at the time, came in the same year, 1976, and I believe that actually was the trigger for going ahead with the vaccine, and there wasn't much human impact, except for the Fort Dix person who died, there wasn't much if any further human-to-human spread, although I do not recall all of the details, and even in the animals they weren't seeing it. So I think there is better understanding of who and how to use surveillance to reduce the uncertainties of when to trigger population interventions, but there remain many uncertainties about when the next pandemic will occur and what impact it will have.

Sandrock: That's a good point.

Muskat: Given the occurrence of these various infectious etiologies over the last 100 years, it is the influenza viruses and SARS-like infections that appear to also be more likely. Are the hemorrhagic fevers something that has occurred much in the United States? What's the incidence, and is that something we really should be on the lookout for?

Sandrock: No, it's extremely low. I've never personally seen a case in the United States. All of the cases we have are imported, and they're very rare, so the only epidemiological risk right now is travel to an endemic area or a laboratory exposure. So with a very small number of cases our clinical practice yields, this disease is not something that is really high on our radar. It does fall into that bioterrorism realm, so it's often lumped together with everything, and that's why we talk about it and teach it, but from a practical standpoint it's very unlikely, and it's one of these things that you hope at least to see coming down the road, because usually when we do see it, it comes from more rural portions of Africa or southeast Asia, and you're going to see this virus creep out of there, and you're going to see cases similar to the way we did with SARS, where we were able to link it with travel relatively early on.

So I think that the incidence is nearly zero and a very low likelihood. It's not high on our radar; we had one suspected case in my tenure in the last 12 years at Davis, and it turned out not to be.

Muskat: Following up on your SARS data, you talked about the avian flu with the one publication, but with SARS 1 out of 10 died. Do you have any idea of how many ventilators were required, how many patients went into respiratory failure out of that group of infected individuals?

Sandrock: I don't offhand, no. That would be a good thing to get.

Rubinson: I believe 20–30% required ICU level care. Just over half of them required mechanical ventilation, but don't quote me on that specific number, but I think 20–30% were considered critically ill.

Sandrock: I don't know the numbers, but Tom Stewart from Toronto[1] has listed some of them, and I think most of it was very similar to avian influenza, that once you got intubated most of those did die, but I don't have the numbers on that side.

1. Hawryluck L, Lapinsky SF, Stewart TE. Clinical review: SARS: Lessons in disaster management. Crit Care 2005;9(4):384–389

Malatino: Interesting that you mentioned smallpox, and hopefully we won't see any smallpox, but recently, earlier this year, we did have a case of a child who had a history of eczema and was exposed to his or her father who was a military person who had had the vaccination. The child deteriorated rather quickly, was ventilated and we sent VIG [vaccinia immune globulin] and the child had some other investigational new drugs[1] that were tried. So we may not see smallpox, but we may see reactions because we have initiated vaccination again, and these people can develop some respiratory problems, as you said, so it is something that we might be seeing—maybe not smallpox but the reactions to the vaccine.

1. Household transmission of a vaccinia virus from contact with a military smallpox vaccinee: Illinois and Indiana, 2007. MMWR Weekly 2007;56(19):478–481. http://www.

cdc.gov/mmwr/preview/mmwrhtmL/mm5619a4.htm. *Accessed August 31, 2007.*

Sandrock: We actually had a case of Sweet syndrome [personal case, unpublished], which was a reaction to drugs, but it looked very much like a pox lesion. I was, unfortunately, the ICU attending physician and the infection-control doctor at my hospital that weekend, and this patient came in and sat in our hallway in our ED for a while, mainly with tachypnea and not really hypoxemic She had the pox-like lesions, and I have never seen a more frenzied response. If you went into the CDC Web site and entered in all the little buttons it started flashing red after we hit return, saying "High risk for smallpox; call the CDC and public health," and it was a very good lesson, but I did certainly learn that the issues can come up with the monkey pox as well, and in the Midwest there was another one that we learned from as well.

Wilgis: I just wanted to see if you can clarify or confirm something. We were doing a pandemic flu workshop about 3 weeks ago in Florida, with hospital, public health folks, University of Florida School of Public Health, Roche, and Red Cross. Dr Stuart Weiss from New Jersey was speaking for us and giving the overview of pandemic flu, where we are today, et cetera. You were mentioning how the virus continues to replicate itself, and there are mistakes as it goes on and on, and H5N1 is looking for the perfect host—one that it can infect but not kill. Dr Weiss stated the Canadian goose has now been determined to be the perfect host, and I was wondering if you had heard anything similar?

Sandrock: Since we have a veterinary school at Davis, I've worked with a lot of those wildlife guys, and it's hard to know which one is the perfect host. I have heard the Canadian Goose as one argument; I've heard a few others mention that as well, and I think it's hard to say. The best way to describe it is that I think you're going to want a bird—and I think part of the reason is that you need something that's going to replicate in the intestine. So in wild birds it actually replicates in the intestines; it's not a respiratory disease until it hits chickens and turkeys. So you want somewhere where it replicates for long periods of time in the respiratory tract—or the intestinal tract. You also want a bird that flies long distances and can spend the summers up north, where the virus can survive, but is willing to fly down to California and these areas for the winter, where the virus can also continue to live. If it stayed in a colder climate, the virus is less likely to survive and spread (when below 40 degrees in the water). So I have heard that argument for the goose in regards to the migration and host factors, but from a molecular and genetic standpoint I have not heard an argument that would support that yet.

Wilgis: It concerned us because the Canadian goose is retired full time in Florida now.

Sandrock: Yes, it's retired along many golf courses in California as well, and they're not very happy about it.

Rubinson: Christian, you highlight that a lot of people present with nonspecific febrile symptoms, and we see that on a daily basis in our units. It almost begets a paradigm shift of infection-control measures to be implemented all of the time, without necessarily stealing Lee [Daugherty]'s thunder. This I think gets to Pete [Muskat]'s point about should we be looking for viral hemorrhagic fever. The problem is that you won't know it until it's there, and that's what we learned from SARS. Once it's in your facility and you're an incubation period behind so you're shutting units down once you (after the fact) figured out that you have a disease that is spreading within your facility.

New Jersey reported a case of Lassa fever several years ago.[1] So I think what all of this tells us is that until we get rapid diagnostics to be able to tell us yes/no immediately when patients are coming in with nonspecific illnesses, we need to rethink how we deal with airway management and respiratory secretions in all high risk respiratory procedures.

1. Centers for Disease Control and Prevention. Imported Lassa fever, New Jersey, 2004. MMWR Morb Mortal Wkly Rep 2004;53(38):894–897.

Sandrock: I fully agree, and that is the underlying thing (and we are probably stealing part of Dr Daugherty's talk), but getting ready and being prepared from that standpoint is paramount. We tried to create an algorithm in our hospital, and I can't say that it's fully followed, but when these patients come in—and from the start—if you don't know what the etiology is and you can't identify it on rapid diagnostics, you isolate these people. We end up getting pneumococcus or H flu or RSV [respiratory syncytial virus] mostly coming out, which is not that big of a deal.

It is very difficult, however, immediately on arrival, so there are rapid diagnostics. You can do a rapid flu test, which is done in an hour, and you can do a Gram stain and look for some of the basic bacterial contents. You may have a couple of clinical features that might single that one patient out so that you don't have to isolate them, but from there we've tried to be very aggressive with isolating these patients, either in droplet precautions, or if we're worried, respiratory isolation. We then also want to be more aggressive with some procedures to make a diagnosis. So if that does mean a bronchoscopy, we go ahead and do it, and get a piece of tissue or a culture result. So it is a paradigm shift from what we normally practice.

It's hard for many of us to think along those terms, because we don't wear masks very long, and every time we go in and out of these rooms, particularly if we're just going to go in and give them a nebulizer treatment or change their circuit on the ventilator or just walk in the room for a second, we don't want to have to put a gown, gloves, and mask on every single time, but it's a habit that we need to get into. Unfortunately, we learned the negative way from SARS and they do that now in Toronto pretty regularly.

Daugherty: We've spent a lot of time talking about avian influenza. The reported case fatality rate, as you have mentioned, is tremendously high. There is some question, though, whether we are missing numerous mild or subclinical infections, giving us total case numbers that underestimate the true burden of disease and overestimate case fatality. Do you have a comment on that?

Sandrock: I actually had a slide, but I cut it out last night when I was looking at it. I was going to put it up there and the exact question is whether the mortality is really over 50%? So the answer is—we don't know, but I think my personal bias as of now is I think that it is closer to 50%. In SARS, initially we thought that it was about 50% because half of the people coming in were getting intubated and dying in the unit, and then we found it was around 11%.

The reason I say this is two-fold. There was one study done by Thorson at the Karolinska University in Stockholm, Sweden.[1] She did a population-based survey and went out and surveyed 45,000 people in a village in Vietnam where there was an outbreak of avian flu and asked questions like "Were you sick?" and "Did you have a respiratory illness during this period of time," if so, "How close were you to the birds?" "What was your relationship with these birds?" and so forth, and found a very nice "dose response." If you handled a sick bird, if you ate that bird, if you processed the bird, you were much more likely to have a respiratory illness. And she concluded that we were missing up to 650 to 750 cases, which would drop our percentage. Now the problem is that it was a population-based survey and they are not the most accurate.

There was a study presented in Cambodia,[2] where they went into a village and found everyone with symptoms, drew their blood, and looked for serology, which is the best standard for influenza exposure. In that study very low rates of transmission were noted. I think it is probably closer to 50%.

1. Thorson A, Petzold M, Nguyen TK, Ekdahl K. Is exposure to sick or dead poultry associated with flu-like illness? A population-based study from a rural area in Vietnam with outbreaks of highly pathogenic avian influenza. Arch Intern Med 2006; 166(1):119–123.
2. Vong S, Coghlan B, Mardy S, Holl D, Seng H, Ly S, Miller MJ, Buchy P, Froehlich Y, Dufourcq JB, Uyeki TM, Lim W, Sok T. Low frequency of poultry-to-human H5NI virus transmission, southern Cambodia, 2005. Emerg Infect Dis 2006;12(10):1542–1547.

Hanley: Other than for SARS and influenza, the concern about most of the other agents you mentioned is their potential for use in bioterrorist activity. Are there scenarios that predict how many patients may end up ventilated if such an attack occurred, for example release of an agent in an enclosed building with 20,000 people, such as a sport complex?

Sandrock: I can just mention one project that we're using, which Lewis [Rubinson] will probably mention, and that is the MIDAS [Models of Infectious Disease Agent Study] project. I'm not the lead person, but a group at Davis just got $600,000 from the Schwarzenegger administration to model hospitals for supplies, which we are doing with Sandia and Cornell now. There are a bunch of models out there to look at that, but we will get to that.

Rubinson: The long and short of it is the models end up being based on so many different assumptions that they can help look at key resource limitations, but sometimes they provide no more "truth" than rational predictions derived on the back of a napkin. That's not to take credit away from people who are trying to really model very complex interactions, but I was just part of a group that probably has our best modelers, and when it comes down to it, they're very helpful, but they're only one tool and clearly not accurate and precise enough to make all policy decisions based on them.

Branson: I appreciate that whole talk. I am just thinking as a respiratory therapist. Is the suggestion now that when I get called to the ED [emergency department] (I don't get called to the ED, by the way) and have to start the patient on NPPV, who's febrile and producing sputum, that therapist should now wear what personal protective equipment?

Sandrock: Elizabeth [Daugherty] will probably get into that more tomorrow. I would use good eyewear or face shield, but in most cases I rarely (unless you think that they may have tuberculosis or something very unusual) put on an N95 mask. I would just put a surgical mask on, and because you are going to have contact with secretions elsewhere, a gown and gloves. Realize that most of these cases are droplet spread, and you can kind of imagine a 3 to 5-foot bubble around the person and that is pretty much about as close as you can go. But it is really tough, and not many of us do this, and I freely admit I don't do this (I say that I am probably about 75% compliant). I am the so-called police officer of our hospital. So I don't do

as great of a job as I can, but it is very difficult.

The CDC just came out with guidelines of every organism and what isolation they should have.[1] It was just on their Web site and we went over it in our infection-control meeting. One of the big surprises that they had was that they lumped in with the severe respiratory illness MRSA, whether it's hospital-acquired or community-acquired, which, as we all know, makes up a good chunk of our patients. But I think if you did wear that at the beginning of the ED, I think you would be pretty safe most of the time.

1. CDC. Guideline for isolation precautions: preventing transmission of infectious agents in healthcare settings 2007. http://www.cdc.gov/ncidod/dhqp/gl_isolation.html. Access 11/6/07.

Branson: My review of the literature about NPPV being dangerous or producing aerosol doesn't seem very strong. What's your opinion?

Sandrock: Yeah, it's case reports and some modeling data. They're a post-experience case-control study where you're going and checking it out and seeing probably what was the risk factor and making a best guess, and you don't always know offhand for certain that that is what did it.

Branson: The final point that I want to make—because it goes towards my talk—just about everything you explained that we might see results in a patient with acute respiratory failure and ARDS, which then dictates what kind of ventilators we have to have.

Media Culture Stock
U.S. Navy Base Hospital, No 1
Brest, France, 1918
Courtesy National Library of Medicine