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## Acute Febrile Respiratory Illness in the ICU\*

### Reducing Disease Transmission

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Acute febrile respiratory illness (FRI) leading to respiratory failure is a common reason for admission to the ICU. Viral pneumonia constitutes a portion of these cases, and often the viral etiology goes undiagnosed. Emerging viral infectious diseases such as severe acute respiratory syndrome and avian influenza present with acute FRIs progressing to respiratory failure and ARDS. Therefore, early recognition of a viral cause of acute FRI leading to ARDS becomes important for protection of health-care workers (HCWs), lessening spread to other patients, and notification of public health officials. These patients often have longer courses of viral shedding and undergo higher-risk procedures that may potentially generate aerosols, such as intubation, bronchoscopy, bag-valve mask ventilation, noninvasive positive pressure ventilation, and medication nebulization, further illustrating the importance of early detection and isolation. A small number of viral agents lead to acute FRI, respiratory failure, and ARDS: seasonal influenza, avian influenza, coronavirus associated with severe ARDS, respiratory syncytial virus, adenovirus, varicella, human metapneumovirus, and hantavirus. A systematic approach to early isolation, testing for these agents, and public health involvement becomes important in dealing with acute FRI. Ultimately, this approach will lead to improved HCW protection, reduction of transmission to other patients, and prevention of transmission in the community.

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**Key words:** acute febrile respiratory illness; ARDS; infection control; respiratory failure; respiratory protection; viral pneumonia

**Abbreviations:** CPR = cardiopulmonary resuscitation; FRI = febrile respiratory illness; HCW = health-care worker; hMPV = human metapneumovirus; HPS = hantavirus pulmonary syndrome; ILI = influenza-like illness; PCR = polymerase chain reaction; PPE = personal protective equipment; RSV = respiratory syncytial virus; RT = reverse transcriptase; SARS = severe acute respiratory syndrome; URI = upper respiratory tract infection; VZV = varicella zoster virus

Febrile respiratory illnesses (FRIs) leading to respiratory failure are common reasons for admission from the community to the ICU.<sup>1,2</sup> Community causes of pneumonia constitute most of these cases,

and up to 11% of all cases of community-acquired pneumonia may progress to ARDS.<sup>3,4</sup> Of concern, many emerging infectious diseases, such as avian influenza (H5N1) and severe acute respiratory syndrome (SARS), present with FRI, acute respiratory failure, and ARDS.<sup>5–7</sup> Early recognition of FRI with respiratory failure is important in order to implement early infection-control strategies to reduce transmission to health-care workers (HCWs) and other patients, as well as to provide detection of pathogens of public health importance.<sup>1,8</sup> ICU patients with FRI and respiratory failure may be more infectious during the early phases of the disease, and these patients frequently require aerosol-generating procedures that can facilitate transmission in the ICU.<sup>2,9–11</sup>

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Early recognition of FRI becomes important in reducing the likelihood of transmission within the ICU to HCWs, visitors, patients, and ultimately the community. Therefore, the approach to a patient with FRI and respiratory failure needs to evolve to include a public health perspective in addition to the focus on individual diagnosis and treatment. A standard approach of early recognition and isolation of FRI followed by early and aggressive diagnostic testing, treatment, and public health involvement is necessary to protect HCWs, patients, and the community from known and unknown emerging infectious diseases.

Unfortunately, the exact etiology for FRI with respiratory failure leading to ARDS is unknown at the time of admission to the ICU. About half of FRIs with respiratory failure are one of the bacteria agents of community-acquired pneumonia, and these can largely be identified shortly after isolation and admission to the ICU with routine culture and testing.<sup>3</sup> Approximately 9% of FRIs in patients admitted to the ICU have a viral origin in prospective studies, and since only a few prospective cohort studies have been performed, a small number of viral etiologies have been documented in the literature.<sup>3</sup> Therefore, early in the course of FRI, care for the patient should focus on appropriate isolation followed by diagnostic testing. If one of the routine bacterial agents of FRI is not identified, diagnostic focus can shift to a possible viral cause. This shift should also involve the public health community, particularly if a known viral pathogen of public health concern is suspected or if viral testing is unsuccessful. Therefore, familiarity with the most common viral pathogens that cause FRIs and respiratory failure with ARDS in normal and mildly immunocompromised (not bone marrow transplant or HIV) hosts, along with their epidemiology, clinical features, treatment, and outcome, becomes important in order to facilitate rapid isolation, testing, diagnosis, and public health involvement.

## VIRAL PATHOGENS

### *Seasonal Influenza*

An acute respiratory illness can be caused by either influenza A or B, often during seasonal outbreaks.<sup>12</sup> With influenza A, three major hemagglutinin subtypes (H1, H2, and H3) with two neuroaminidase subtypes (N1 and N2) have been described in humans with frequent antigenic drift in these glycoproteins.<sup>12</sup> Influenza B has less propensity for antigenic shift, and a few genetic drifts in the hemagglutinin have been described allowing for seasonal variability.<sup>12</sup> Both influenza A and B circu-

late yearly, with influenza A beginning more abruptly and influenza B cases being more predominant in the later part of the season. However, regional differences exist, with more B strains found in Europe and Asia. Influenza B is more common in long-term care facilities, schools, or other institutions.

Most cases of influenza are self-limiting infections with nonspecific symptoms such as fever, headache, myalgias, and malaise (an influenza-like illness [ILI]).<sup>12,13</sup> Traditionally, influenza B has a more mild and self-limited course, but this difference cannot be determined on clinical grounds alone and requires laboratory confirmation. However, a smaller number of individuals with both influenza A or B, particularly higher-risk individuals (Table 1), are likely to have a primary pneumonia.<sup>13-16</sup> The respiratory symptoms will persist or progress, and in a minority of cases ARDS can develop. This occurs in individuals at higher risk and with chronic pulmonary disorders, but healthy individuals with this progression have been described as well. The majority of deaths during a seasonal outbreak occur from primary pneumonia or secondary bacterial pneumonia.<sup>12</sup>

During a seasonal outbreak, diagnosis can be made clinically with good reliability because a combination of fever and cough had a 79% positive predictive value.<sup>12,13</sup> More definitive diagnosis can be made by viral detection in nasopharyngeal aspirate, swab, or lower respiratory tract sample in a patient with appropriate clinical symptoms, with subtyping done by polymerase chain reaction (PCR) in public health laboratories (Table 1).<sup>12</sup> Rapid influenza viral diagnostic tests using immunofluorescence or enzyme immunoassays provide rapid, reliable testing and can detect influenza A or B strains. However, viral shedding peaks at 48 h of illness and declines thereafter. Thus, PCR testing of a lower respiratory tract sample for FRI with ARDS may be more beneficial. Additionally, subtyping of a suspected case of influenza-related FRI with ARDS requires virus isolation that should be sent to a public health laboratory.

Treatment of influenza can be undertaken with agents from two antiviral classes: the adamantanes and neuroaminidase inhibitors.<sup>17</sup> Due to widespread resistance to most adamantanes, use of these drugs should be reserved for cases or outbreaks with known susceptibility (Table 1). Studies<sup>17</sup> with the neuroaminidase inhibitors show a reduction in symptom time and viral shedding, with best effect seen when the drug is started within 48 h of symptom onset. Treatment with neuroaminidase inhibitors after 48 h may provide some additional benefit but have not been fully studied. Viral resistance to neuroaminidase inhibitors is low within the community.

**Table 1—Main Features of Viruses That Cause Severe Pneumonia and ARDS**

Variables	Seasonal Influenza	Avian Influenza	SARS	RSV	Adenovirus	VZV	hMPV	Hantavirus
Virus family	Orthomyxoviridae	Orthomyxoviridae	Coronavirus	Paramyxoviridae	Adenovirus	Herpes	Paramyxoviridae	Bunyaviridae
Usual clinical syndrome	Influenza	Conjunctivitis, pneumonia	Pneumonia	URI	URI	Chicken pox	URI	Cardiopulmonary syndrome
High-risk groups for severe pneumonia	Elderly, infants	All groups	Elderly	Immunocompromised, elderly	Institution, immunocompromised	Pregnancy, adults, smokers	Immunocompromised	None
Epidemiologic risk	Winter season or travel	Contact with sick, dead birds and poultry	Contact with known individuals	Winter season	Military camps, mental health facilities	Contact with infected individual	None known	Contact with dead rodents or products
Clinical or laboratory characteristic	ILI, lack of rhinorrhea,	ILI, rapid progression to respiratory failure	Rapid progression to pneumonia after fever	Preceding URI	Preceding URI with conjunctivitis	Vesicular rash	Preceding URI	Thrombocytopenia, leukocytosis, elevated hematocrit
Mode of transmission	Droplet, contact	Droplet, contact, airborne	Droplet/airborne, fecal-oral	Droplet, contact	Droplet, contact	Droplet, contact with vesicles	Unknown, but droplet and contact suspected	Rodent products
Isolation required	Droplet	Airborne and contact initially, droplet possible	Airborne	Droplet and contact	Droplet and contact	Droplet and contact	Droplet	None
Diagnostic testing	Antigen assay, viral culture, RT-PCR	RT-PCR	RT-PCR	Antigen immunoassay, viral culture, RT-PCR	RT-PCR	Histopathology, viral culture, antigen assay	RT-PCR	Serology
Treatment	Oseltamivir, zanamivir	Oseltamivir, zanamivir	Supportive, maybe steroids	Ribavirin	Supportive	Acyclovir	Supportive	Supportive
Mandatory public health notification	No	Yes	Yes	No	No	No	No	Yes

**Table 2—Higher-Risk Procedures in Viral Respiratory Tract Infections**

Nebulization of medication
Endotracheal intubation
Nasotracheal suctioning
Noninvasive positive pressure ventilation
Bag-valve mask ventilation
CPR
Bronchoscopy
Humidified oxygen delivery
Nonrebreather mask without expiratory filter

Influenza should be suspected during the winter epidemic season or if travel to an endemic area has occurred.<sup>12</sup> Transmission is primarily by droplets and contact with respiratory secretions, so patients suspected of influenza infection should be placed in droplet isolation, and HCWs should wear surgical masks, face shields, eye protection, gowns, and gloves as the appropriate personal protective equipment (PPE).<sup>2,18,19</sup> If a novel strain has been detected by laboratory testing, HCWs should wear an N-95 mask, and the patient should be placed in airborne isolation instead until mechanism of transmission is further understood.<sup>20</sup> Based on the SARS experience, higher-risk procedures generating aerosols (Table 2) may require the use of an N-95 mask or a powered air-purified respirator.<sup>2,5,7,9</sup>

### Avian Influenza

Avian influenza A infections in humans have been increasing in incidence over the past decade.<sup>17</sup> These infections are caused by avian subtypes of influenza A, usually H5, H7, and H9. Most patients report contact with sick or dead poultry, although a few human-to-human cases of transmission have occurred.<sup>17,21,22</sup> Most subtypes present with conjunctivitis, but the highly pathogenic H5N1 subtypes present with severe primary pneumonia with respiratory failure and ARDS (Table 1).<sup>6,17,23–28</sup> Respiratory failure with multiorgan damage is seen in > 60% cases, and the total mortality rate is > 60%.<sup>29</sup> Once admitted to the ICU with respiratory failure, the mortality rate is > 90%. This observed mortality represents clinical patients who sought health care, and population-based questionnaire surveys suggest that milder and even subclinical infections may exist, thus likely significantly lowering the case fatality rate.<sup>30</sup> Diagnosis is by reverse transcriptase (RT)-PCR (viral isolation requires a biosafety level 3 laboratory) in a patient with appropriate clinical symptoms and epidemiologic risk factors and should always involve public health officials.<sup>31</sup> Treatment is supportive with addition of a neuroaminidase inhib-

itor. The largest treatment experience has been with oseltamivir, and reduction of virus in nasal washings has been demonstrated.<sup>17,32,33</sup> Resistance has been demonstrated, largely due to a point mutation and change in a histidine to tyrosine within the neuraminidase receptor.<sup>33</sup> *In vitro* testing with a few strains has shown that this resistance can be overcome with higher doses of oseltamivir, but larger studies have not been performed. Additionally, resistance is not conferred to zanamivir.

Most cases are initially detected by the epidemiologic link of contact with sick and dead birds. Transmission is likely droplet, but airborne transmission has been proposed by some officials, prompting higher levels of protection.<sup>20</sup> Ingestion of undercooked poultry and swimming with infected waterfowl have also been suspected as routes of human infection. Isolated cases of avian influenza in humans will be managed differently than pandemic influenza, with suspected patients being initially placed in airborne isolation and all HCWs wearing N-95 masks or other appropriate levels (powered air-purified respirator) of protection.<sup>20</sup> Isolated cases of human-to-human transmission have probably occurred among HCWs, but in all cases the appropriate PPE was not used.<sup>17,21,22</sup> Aerosol-generating procedures should be reduced if possible (Table 2). Finally, any suspected case of avian influenza should prompt an urgent notification to local public health officials so that H5N1 infection can be verified and community measures to reduce spread can be instituted.

### SARS

SARS is caused by a novel coronavirus that was first detected in 2003.<sup>5,7,34</sup> Thousands of cases occurred worldwide in the initial epidemic in 2003, but the epidemic abated and new cases have not been reported since.<sup>34</sup> The clinical presentation is characterized by fever, chills, rigors, malaise, nausea, and shortness of breath (Table 1).<sup>5,7,35</sup> The symptoms occurred on average 7 days after contact. Pneumonia appeared to develop approximately 8 days after onset of fever, with 45% of patients having hypoxemia. Approximately 20% of cases went on to severe lung injury and ARDS requiring mechanical ventilation.<sup>7,11,35</sup> Development of ARDS from onset of fever is bimodal, with peaks at 11 days and 20 days. The global fatality rate was 11%, with most deaths in patients > 65 years old.<sup>7,11</sup> No deaths were reported in children.<sup>7</sup> Diagnosis includes an ILI with severe pneumonia in the presence of the epidemic or laboratory exposure with viral detection by RT-PCR in respiratory samples (Table 1).<sup>5,7,11,36</sup> A serum immunofluorescence assay may detect cases long after onset, and the only public health laboratory that

performs these tests is at the Centers for Disease Control and Prevention. Treatment is largely supportive, but steroids were used in some cases after the development of ARDS.

Initial cases in 2003 were difficult to identify, which resulted in extensive spread to HCWs. Spread is by droplet transmission, although many cases suggest that airborne and contact routes also occur, and outbreak analysis has not ruled out oral-fecal spread as well.<sup>2,37</sup> Spread to HCWs who wore appropriate PPE suggests airborne spread, and additional spread by aerosol-generating procedures such as cardiopulmonary resuscitation (CPR), intubation, medication nebulization, and noninvasive positive pressure ventilation.<sup>9,10,37-41</sup> The experience with SARS, particularly among HCWs, supports an approach to care requiring early isolation and enhanced PPE when engaging in certain higher-risk procedures (Table 2).<sup>2,20</sup> 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 epidemiologic risk. Therefore, any consideration of SARS or another potential virus should promptly be reported to hospital infection control and public health officials.<sup>20</sup>

### *Respiratory Syncytial Virus*

Respiratory syncytial virus (RSV) causes acute respiratory tract infections in all ages and is the most common cause of lower respiratory tract infections in children < 1 year of age.<sup>42-44</sup> In adults, RSV infections developed in 3 to 7% of elderly adults and were even higher in high-risk groups.<sup>42,43,45</sup> Infection follows a pattern similar to influenza, with epidemics occurring in the winter months. Adult infections are manifested predominately by upper respiratory tract symptoms, but some patients will have lower respiratory tract infections, including bronchiolitis, pneumonia, bronchospasm, and acute respiratory failure and ARDS (Table 1).<sup>43,46,47</sup> Lower respiratory tract disease usually occurs with primary infection in children but can occur with recurrent infections into adulthood. The elderly and immunocompromised, particularly bone marrow transplant patients, are at highest risk of respiratory failure. Diagnosis is by clinical findings during an epidemic period with rapid antigen assays, viral isolation, or RT-PCR detection.<sup>48</sup> Treatment for bronchospasm includes bronchodilators and steroids, with ribavirin for severe and high-risk cases.<sup>49</sup> However, one recent randomized control trial<sup>50</sup> evaluated children < 12 months of age with moderate-to-severe bronchiolitis in which the majority of cases (> 60%) were caused by RSV; the results showed that a single dose of

dexamethasone did not alter admission rates, length of stay, and respiratory status. Overall, 15% of patients with infections are admitted to the ICU, and the mortality rate can be surprisingly high, at 10% of all cases in the elderly.<sup>42,43,45</sup>

Infection rarely occurs outside of the winter months unless travel to an epidemic area occurred. Spread is largely by contact and droplet transmission, with contact transmission playing a significant role when compared to other respiratory viruses.<sup>43,47</sup> Therefore, hand washing greatly reduces the spread of RSV in addition to droplet isolation and the appropriate PPE. Viral shedding lasts 3 to 5 days on average, but higher-risk individuals in the ICU (immunocompromised, solid-organ transplant, and the elderly) may shed longer. Isolation should continue until 24 h after the cessation of fever.

### *Adenovirus*

Adenovirus is one of the most common causes of upper respiratory tract infections (URIs) in adults and children.<sup>51,52</sup> However, severe lower respiratory tract disease has been described in healthy and at-risk individuals, particularly in military and other institutional settings.<sup>53,54</sup> Pneumonia and ARDS develop in a minority of individuals and usually are associated with conjunctivitis and other extrapulmonary manifestations such as GI disease, hepatitis, meningitis, and hemorrhagic cystitis.<sup>53-55</sup> Extrapulmonary complications, along with ARDS, are more frequent in transplant recipients.<sup>52</sup> Pneumonia and ARDS appear to be more common with subtype E type 4 and subgroups B type 7. Serogroup 35 has been documented in long-term health facilities, such as mental health facilities.<sup>52-54</sup> Diagnosis is made by antigen assay or PCR, but viral culture is preferred for severe pneumonia and institutional outbreaks because serotyping is desired (Table 1).<sup>52</sup> Treatment is largely supportive, although cidofovir and ganciclovir have some activity *in vitro*.<sup>52</sup> In the past, vaccination for military recruits was against serotype 4 and 7, which constituted > 60% of the cases of pneumonia<sup>55</sup>; however, in 1999, the sole producer of this vaccine stopped production, and the military no longer routinely vaccinates recruits.

Contact with infected fomites plays a large role in transmission because adenovirus remains viable on environmental surfaces for long periods of time.<sup>51,53-55</sup> Some amount of droplet transmission also occurs, and the virus has a long period of shedding in transplant patients.<sup>52</sup> Therefore, aggressive decontamination of environmental surfaces along with contact and droplet precautions are indicated.<sup>51,53-55</sup>

Public health officials should be contacted in any cases involving an institutional setting or if serotyping is desired.

### *Varicella-Zoster Virus*

Varicella-zoster virus (VZV) infection causes acute and recurrent febrile illness, followed by malaise, pharyngitis, and a vesicular rash.<sup>56,57</sup> Primary disease occurs throughout the year and is usually benign in immunocompetent individuals, with recurrent disease seen more in immunocompromised adults. Pneumonia develops with primary infection, occurs rarely in children, and progresses to respiratory failure and ARDS.<sup>58–62</sup> Pneumonia is the most frequent serious complication of VZV infection in adults, with an incidence of approximately 20% in primary VZV. Risk factors for pneumonia with respiratory failure and ARDS include pregnancy, smoking, and immunosuppression.<sup>63,64</sup> Pneumonia and respiratory failure develop slowly, usually a few days after the onset of rash, and are signaled by tachypnea and hypoxia.<sup>56,58,61,62</sup> Additional complications include encephalitis, hepatitis, and secondary skin and soft-tissue infections.<sup>58–62</sup> The overall mortality rate for VZV pneumonia remains high at 30%; in patients requiring ICU admission and mechanical ventilation, the mortality rate approaches 50%. Clinical examination yields the diagnosis in many cases because vesicular rash accompanies any pulmonary disease. Confirmation of diagnosis is done by viral isolation and culture, immunosorbent assay, or pathologic findings on biopsy. Treatment including acyclovir and corticosteroids has been shown to lessen hospital and ICU stay but not alter the mortality rate.<sup>59,65</sup> The routine use of the vaccine has altered typical presentation, with some children having breakthrough infections after only a single dose.<sup>66</sup> These infections usually are less severe, produce < 50 lesions on average, and rarely present with pneumonia, but immunity appears to wane after 5 years. Recent recommendations<sup>66</sup> call for a second booster dose of the vaccine within 5 years of the first.

Spread is by direct contact with skin lesions, but in the case of primary infection and pneumonia, droplet transmission is also an important route.<sup>57</sup> The infective period can be long, from onset of fever prior to the rash until all lesions have crusted and the pneumonia has improved.<sup>57,61,62</sup> Therefore, HCWs and family members who do not have immunity from prior infection must avoid contact. If contact with infected patients must occur, protective equipment including gown, gloves, mask, and eye protection must be worn.<sup>57</sup> Vaccination of the nonimmune HCW should also be performed to reduce risk of transmission if they have no prior history of disease.<sup>67</sup> Pregnant HCWs are at risk due to the

increased likelihood of primary varicella pneumonia, ARDS, and the effects of VZV on the fetus.<sup>63,64</sup> Thus, pregnant staff cannot care for patients with active VZV. However, if contact occurs, the infection control specialist should be consulted.

### *Human Metapneumovirus*

Human metapneumovirus (hMPV) has worldwide distribution and is one cause of respiratory tract infections, although its incidence and epidemiologic features remain largely unknown.<sup>68,69</sup> The virus was first detected in 2001 and has now been described in children and adults in a late winter-to-spring seasonal variability. One study<sup>69</sup> suggests that > 45% of cases of respiratory disease come from adults > 65 years old, causing approximately 5% of all respiratory infections. However, the extent of respiratory disease in adults is unknown and largely comes from population-based studies, not prospective cohort studies. Adult symptoms appear to include a self-limited cough, nasal congestion, and rhinorrhea, but immunocompromised adults can have lower respiratory tract infection with respiratory failure.<sup>68–70</sup> Progression, however, does appear rare, and no cases have been described in immunocompetent adults, and the only significant risk for progression to respiratory failure appears to be transplantation. Diagnosis is difficult because no reliable commercial assays are available, so detection is largely done by PCR on respiratory specimens. Viral culture can be easily obtained as well, but identification usually is done by public health laboratories. Treatment is supportive, especially since most cases are self limited.<sup>68–70</sup> The mortality rate for infection with respiratory failure and ARDS is unknown, but deaths in bone marrow transplant patients have been reported.<sup>70</sup> Transmission is largely unknown because no formal studies exist, but contact and droplet transmission is suspected.<sup>68</sup> Although the extent and spectrum of hMPV disease is largely unknown, any suspected case in an adult with ARDS and respiratory failure should have respiratory samples sent to the public health laboratory for further investigation.

### *Hantavirus*

Hantaviruses are part of a larger genus that contains > 20 viral species. This genus causes two severe acute febrile illness, hemorrhagic fever with renal syndrome, found in the Old World, and hantavirus cardiopulmonary syndrome (HPS), found in the New World.<sup>71–73</sup> In North America, the disease has been largely reported in the Southwest and California, with cases reported in Canada, Europe, China, Chile, Argentina, and other parts of South America.<sup>74</sup>

Cyclical outbreaks tend to occur when the rodent population increases.<sup>75</sup> Symptoms initially begin with fever, chills, and myalgias in a prodromal phase.<sup>71–73,75</sup> There is a lack of upper respiratory symptoms because the disease progresses rapidly to dry cough, respiratory failure, and ARDS, shock, coagulopathy, and arrhythmias. Resolution can also occur rapidly. Notably, thrombocytopenia with a immunoblast-predominant leukocytosis and an elevated hematocrit are characteristic of the early cardiopulmonary phase.<sup>76</sup> Diagnosis is by serologic testing of IgM in early disease and IgG in later disease through public health laboratories. Clinical contact with rodents in an endemic area with leukocytosis, elevated hematocrit, and thrombocytopenia should prompt consideration of the diagnosis. Treatment is mainly supportive, with extracorporeal membrane oxygenation being used in some patients<sup>71,73</sup>; ribavirin has been effective in hemorrhagic fever renal syndrome but not HPS. The mortality rate remains at approximately 20%.

Transmission of hantavirus occurs through contact with rodent excrement (particularly urine) when the virus is aerosolized.<sup>71–73</sup> This mostly occurs in indoor settings where dead rodent and rodent urine are present. Direct live rodent contact has not been implicated in transmission, and no human-to-human transmission has been documented with HPS. Confirmed hantavirus infection should be reported to public health officials.

#### INITIAL MANAGEMENT AND TESTING OF FRIS WITH RESPIRATORY FAILURE AND ARDS

In most cases, the etiology of a febrile respiratory illness is largely unknown on admission to the ICU.<sup>34</sup> Bacterial pathogens constitute most cases, and they often can be suspected early based on clinical findings and Gram stain of the sputum. Other cases may be more difficult, requiring further epidemiologic and diagnostic testing. Recent guidelines<sup>4</sup> have suggested that testing for viral pathogens be performed in patients with clinical and epidemiologic findings suggestive of viral illness, as well as placing them in droplet or airborne isolation depending on the suspected pathogen. However, many of these viral pathogens are highly contagious emerging infections or in fact may be novel strain.<sup>7,35</sup> Often these patients will not be isolated and tested for these pathogens on hospital admission, and they will additionally undergo higher-risk aerosolizing procedures (Table 2) that will increase the likelihood for disease transmission. This puts both HCWs and other patients at risk for acquiring disease, as experienced during the SARS epidemic. Therefore, a

standardized approach, with early isolation and testing of these cases, can reduce the likelihood of disease transmission of an emerging pathogen within the ICU.

Figure 1 outlines an approach to early isolation, testing, and involvement of institutional infection control, infectious diseases, and public health in patients with FRI and respiratory failure admitted to the ICU. All patients with FRI and respiratory failure should immediately be isolated on arrival to the health-care system, and 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 radiography), targeted treatment and ICU admission are 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 as often seen with viral causes of FRIs, the patients should remain in isolation and further diagnostic testing should be performed. Isolation should most likely be droplet, but based on specific epidemiologic clues airborne isolation may be instituted (Table 1).<sup>20</sup> Many cases of viral pneumonia in the ICU are suspected based on certain at-risk groups, epidemiologic clues, and specific clinical findings. If these are present, testing should target these pathogens, but viral culture and isolation should be performed to rule out other agents as well. If a certain viral pathogen, such as avian influenza or SARS, is suspected based on these clues, hospital infection control, infectious diseases, microbiology, and the public health officials should be notified immediately. Although bronchoscopy generates aerosols and can increase transmission risk, it should not be avoided in these cases because viral isolation and etiology becomes important from a public health perspective and transmission risk is low when the appropriate PPE is used. Isolation of the virus from a nasopharyngeal swab or aspirate is highest early in disease course, but by the time the patient has disease developed in the lower respiratory tract with respiratory failure, a lower respiratory sample by bronchoscopy may provide the highest yield. In addition to more specific testing, a sample should be sent for viral culture, which provides a viral isolate for further testing, subtyping, and resistance analysis if ever indicated (unless avian influenza is suspected, since this requires a biosafety level 3 laboratory). Patient isolation should remain until a diagnosis is established or the patient improves, remaining afebrile for at least 48 h. Any change in isolation status should involve an infection control and infectious disease specialist.



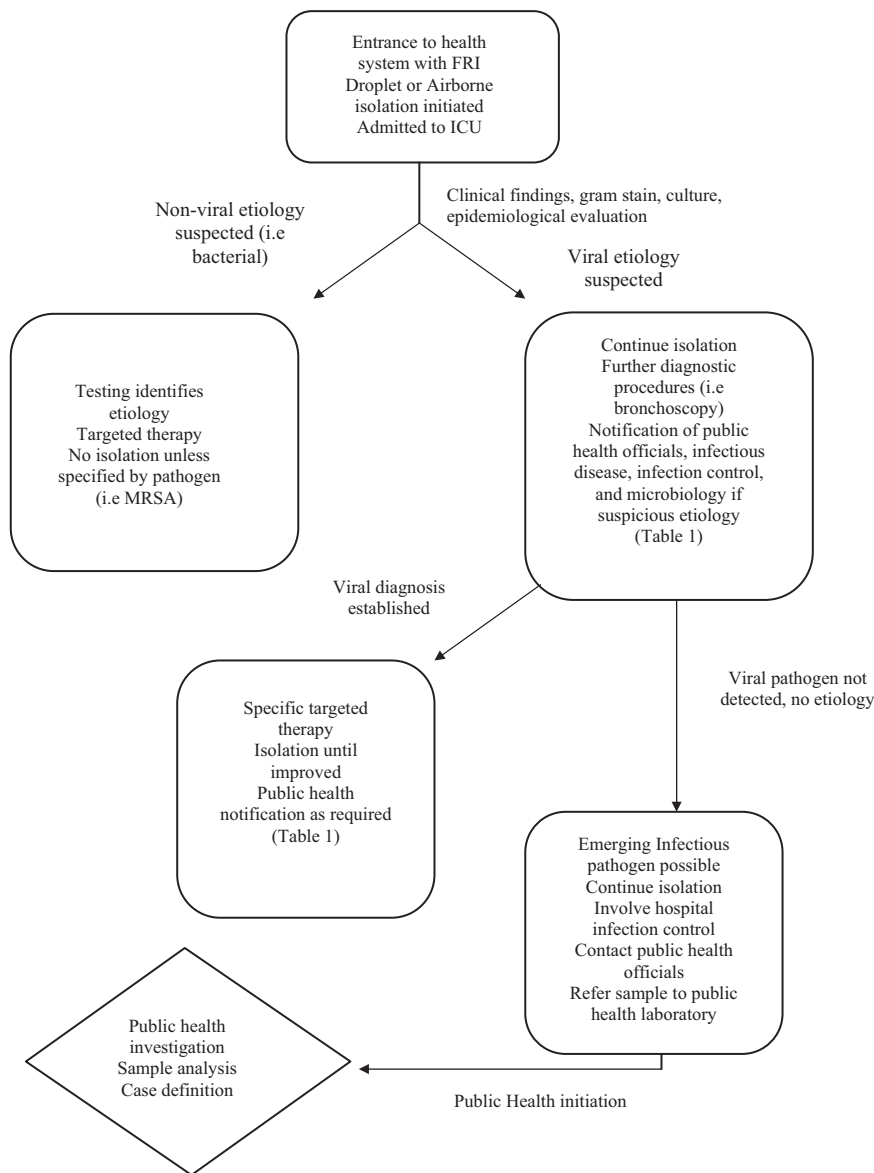


FIGURE 1. Standardized approach to patients with an acute FRI in the ICUs in order to enhance diagnosis, reduce transmission, and involve public health officials. MRSA = methicillin-resistant *Staphylococcus aureus*.

Involvement of institutional infection control, infectious disease specialist, microbiology, and public health is paramount for successful containment of disease and thus should be started as early as possible, as outlined in Figure 1. Hospital-based infection control will assist in isolation and HCW protection, and the hospital-based microbiology laboratory should be notified of suspected pathogens, allowing for worker protection and targeted testing of samples. Public health involvement will allow a broader viral testing, including additional agents, subtyping, and resistance testing. If the agent is a novel or emerging pathogen, as seen with SARS or avian influenza, early public health involvement will allow for rapid

laboratory testing, epidemiologic investigation, case definition, and community prevention. Finally, public health also has a broader view of the disease burden within the region. A single physician seeing a patients with FRI and ARDS may not be aware of multiple other cases within the region, and thus involvement of public health allows this broader perspective.

Finally, aerosol-generating procedures are most common in ICU patients with FRI and respiratory failure, and HCWs are thus at high risk for exposure to these pathogens. However, most cases of transmission during aerosol-generating procedures, such as CPR and bag-valve mask ventilation, are based

largely on epidemiologic and case studies, and direct studies are lacking. Yet, appropriate PPE should be worn by HCWs at all times; 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 HCWs did not wear the appropriate PPE, which appears to be the largest risk factor for transmission to the HCW.<sup>2,25</sup>

## CONCLUSION

The approach to patients with an acute FRI and respiratory failure can be challenging. In addition to the management of each individual patient's critical illness, management needs to include an institutional and public health perspective. Early testing and isolation for potentially contagious patients can reduce transmission to HCWs, patients, and the community. Only a small number of viral pathogens are likely to produce respiratory failure and ARDS, so targeted testing can often achieve diagnosis. Early communication with public health officials is very important because they can assist with more complex diagnosis and disease investigation, enhancing the diagnosis and reducing the risk of transmission. Finally, all HCWs should wear appropriate PPE at all times, reducing the risk of disease transmission in these high-risk patients.

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