Respiratory syncytial virus Infection among Intubated Adults in a University Medical Intensive Care Unit*

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Respiratory syncytial virus is the major cause of lower respiratory tract infection in children. Adults who are immunocompromised, aged, institutionalized, and/or have underlying medical diseases may be at risk for severe RSV infection. Intubated adults in an MICU were evaluated for evidence of RSV infection. Respiratory secretions were analyzed by cell culture and RSV EIA. Serologic testing was obtained. Respiratory secretions from MICU personnel with acute respiratory symptoms and patients admitted for pneumonia, asthma, or COPD also were screened. Five of 11 intubated patients had evidence of RSV infection. One of seven MICU employees and four of 48 ward patients had RSV-positive respiratory secretions. During community outbreaks of RSV infection, adults admitted to an MICU already may be infected with RSV; those admitted for other reasons are at risk for nosocomial infection. Patients occupying other hospital units and personnel may be instrumental in the nosocomial dissemination of RSV.

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CABG = coronary artery bypass graft; CF = complement fixation; EIA = enzyme-linked immunosorbent assay; HSV = herpes simplex virus; IFA = immunofluorescence assay; MICU = medical intensive care unit; PICU = pediatric intensive care unit; RSV = respiratory syncytial virus

Respiratory syncytial virus is the major cause of lower respiratory tract infection in young children and infants. Significant yearly outbreaks of RSV activity have been reported worldwide, usually occurring in winter or spring. Primary infection is essentially universal by early childhood. Incomplete immunity occurs permitting reinfection throughout life. RSV infection in previously healthy adults typically results in mild respiratory symptoms, although altered airway resistance can occur, which may persist for weeks. It is now recognized that adults who are immunocompromised, institutionalized, aged, and/or have underlying medical diseases, especially COPD, may be at risk for severe RSV infection.

Respiratory syncytial virus is also an important nosocomial pathogen in the very young and the elderly. Nosocomial transmission of RSV among patients and personnel on pediatric wards is well characterized. Hospital-acquired RSV disease has been described in pediatric and neonatal intensive care units. Nosocomial RSV pneumonia in a hospitalized elderly patient with COPD has been reported. Individuals residing in chronic care facilities and hospitalized immunocompromised adults also may be at risk for nosocomial infection.

Subsequent to the diagnosis of RSV infection in a critically ill intubated adult, this study was instituted to investigate prospectively the incidence of RSV infection among intubated adults in a university MICU during the 1988-1989 community outbreak.

Methods and Materials

This survey was conducted in the eight-bed MICU at LSU Medical Center, a 500-bed facility which serves a population of approximately 1 million people. The MICU and PICU share a corridor. Patients are in individual rooms and there is no cross-coverage by medical or nursing personnel. Only respiratory therapists provide care to both MICU and PICU patients.

All intubated adults were eligible for the study between January 12 and March 3, 1989, a time when RSV was prevalent in the pediatric population of our community (Fig 1). Patients admitted previously to the MICU were enrolled in the study if they remained intubated on January 12. Respiratory secretions were collected into in-line plastic traps during routine suctioning of intubated patients. If secretions were minimal, a 5-ml saline lavage was performed and the aspirate was collected for testing. Specimens were transported immediately to the LSU Diagnostic Virology Laboratory. A portion of the sample was tested for RSV antigen using EIA (Kallestad; sensitivity, 87 to 93 percent). The remainder was inoculated into human foreskin fibroblasts, green monkey kidney cells, and human epidermoid carcinoma cells for viral isolation. Respiratory secretions from each patient were retested weekly. Sera were collected during the acute phase of illness for analysis of antibody by CF for RSV, adenovirus, influenza A and B, and HSV; EIA was utilized to detect antibody to cytomegalovirus and Mycoplasma pneumoniae (Louisiana State Health Department, New Orleans). Additionally, sera were tested for RSV antibody by IFA (Mayo Clinic Laboratories, Rochester, MN). When feasible, sera were obtained during the convalescent period within 8 to 13 weeks.

The PICU and Diagnostic Virology Laboratory records were reviewed to determine the number of RSV-infected children admit-
ted to the adjacent PICU during the study interval. All intensive care unit personnel with acute respiratory symptoms were asked to submit respiratory secretions and sera. Asymptomatic employees were omitted because adults with repeated RSV infection rarely manifest subclinical disease. Respiratory secretions were collected in tissue by nose blowing with transfer of secretions into saline solution. If minimal secretions were present, a cotton-tipped wooden swab was passed through the anterior nares to the posterior pharynx and twirled. The swab was doused in 1 ml of saline solution. Collection was repeated until the saline solution was turbid. Respiratory secretions were obtained soon after admission from all adults hospitalized on the general medicine wards with the initial diagnosis of pneumonia, asthma, or COPD. Most specimens from these individuals were collected by nasal swab as described previously.

This study was approved by the LSU Institutional Review Board, and informed consent was obtained from each participant.

RESULTS

Of 62 adults admitted to the MICU during the study interval, 18 were intubated and specimens were collected from 11. The remaining seven were not included because of lack of informed consent, death soon after admission, or inability to obtain sufficient specimen material. Five (45 percent) of the eleven intubated patients demonstrated laboratory evidence of RSV infection, four by EIA and one by viral isolation in cell culture. During the study interval, six children were hospitalized in the adjacent PICU with community-acquired RSV infection. Of seven MICU employees with acute respiratory symptoms who submitted respiratory secretions for testing (three physicians, one nurse, one medical student, one respiratory therapist, one nursing aide), one, a physician, had evidence of RSV by viral isolation in cell culture.

Hospitalizations of the six RSV-positive children in the PICU and the 11 intubated adults studied in the MICU are represented in Figure 2. Patient 2 was the first adult in the MICU with evidence of RSV infection and initiated our interest in screening for RSV in the critically ill. Because this patient had been hospitalized for 13 days prior to the diagnosis of RSV, nosocomial acquisition was presumed, since the incubation period for RSV in immunocompetent adults is usually from two to eight days. Interestingly, he had been hospitalized first in a ward and then in the MICU of another hospital for six and three days, respectively, prior to admission to the LSU MICU. Due to a prolonged MICU hospitalization for patient 1 prior to diagnosis of RSV infection, nosocomial acquisition likewise was presumed. This patient had had a tracheostomy for two months at the time of diagnosis of the RSV infection. Patient 4 had confirmed nosocomial RSV infection because she had a negative RSV screen documented prior to becoming RSV-positive. Due to a bed shortage, this patient was transferred to another local MICU on day 6 of her hospitalization and returned to LSU MICU on day 11. Patients 5 and 8 manifested community-acquired RSV infection as they screened positively for RSV shortly after admission.
**Figure 2.** The upper portion of the graph delineates sequence of admission and duration of each PICU hospitalization for the six children with community-acquired RSV infection. Similar data are shown in the lower portion for the 11 MICU patients studied. Patients 1, 2, 6, and 11 were hospitalized 6, 6, 1, and 3 days, respectively, prior to intubation. Dates of RSV-positive specimens appear beneath RSV+ on horizontal lines. Patients 1, 2, and 4 likely manifested nosocomial RSV infection. The date at the far right of each bar denotes death or discharge from intensive care unit.

Patient 2 was first positive for RSV 17 days before the MICU physician became symptomatic. Patients 1 and 4 acquired RSV at a time when this physician was RSV-positive. The MICU physician's young children had recently been ill with undefined febrile upper respiratory tract infections.

Table 1 lists demographic features, underlying diseases, reasons for intubation, total number of MICU days, number of days intubated, the day of RSV testing in the MICU, RSV-EIA and cell culture results of respiratory secretions, and mortality. None of the participants received significant immunosuppressive therapy. All RSV-positive patients had at least one underlying medical disease. Though RSV-positive patients tended to be older and have longer hospital stays, the difference did not reach statistical significance. None of the five RSV-positive intubated adults had significant bacterial isolates from their blood or endotracheal aspirates. In patient 2, HSV was isolated on the last day of life. Four of the five had an infiltrate present on chest radiograph.

Among RSV-negative patients, the occurrence of significant bacterial disease at the time of admission was documented in four (patients 6, 7, 9, and 10). In two of these patients, viral and/or fungal isolates also were present. Respiratory secretions from patient 6 were culture-positive for HSV just prior to death. In patient 9, a lung biopsy revealed interstitial pneumonitis and was culture-positive for HSV. Bacterial cultures of her tracheal aspirate yielded *Candida albicans* and *Cryptococcus neoformans*. This patient was subsequently found to have acquired immunodeficiency syndrome and had been diagnosed and treated 12 years previously for squamous cell carcinoma of the vagina. All RSV-negative participants had an infiltrate demonstrated by chest radiograph.

Serum was available from four RSV-positive and five RSV-negative patients, the RSV-positive physician, and three RSV-negative employees. None demonstrated antibody to RSV by CF. All sera were positive by RSV-IFA for IgG, however, in every person in whom sera from the illness and convalescent periods were tested, high, unchanging titers were detected (Table 2). Patient 1, who was RSV-EIA-positive, had RSV-specific IgM in the serum obtained during illness, suggesting recent infection. Patients 5 and 7 each had a fourfold
<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Age (yr)</th>
<th>Sex/Race*</th>
<th>Underlying Disease</th>
<th>Reason for Intubation</th>
<th>Total MICU Days†</th>
<th>Total Days Intubated</th>
<th>Hospital Days Tested</th>
<th>RSV-EIA</th>
<th>Viral Culture</th>
<th>Patient Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>RSV-Positive</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>54</td>
<td>F/W</td>
<td>Diabetes mellitus, coronary artery disease</td>
<td>Cardiopulmonary arrest 12 days after CABG</td>
<td>96(6)</td>
<td>94</td>
<td>98</td>
<td>+</td>
<td>. . .</td>
<td>Died</td>
</tr>
<tr>
<td>2</td>
<td>50</td>
<td>M/B</td>
<td>Renal failure, alcoholism</td>
<td>Respiratory failure 2° to pneumonia</td>
<td>25(6)</td>
<td>25</td>
<td>13</td>
<td>+</td>
<td>NT</td>
<td>Died</td>
</tr>
<tr>
<td>4</td>
<td>58</td>
<td>F/W</td>
<td>COPD, alcoholism</td>
<td>Respiratory failure 2° to pneumonia</td>
<td>33</td>
<td>29</td>
<td>2</td>
<td>. . .</td>
<td>Survived</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>64</td>
<td>F/W</td>
<td>Diabetes mellitus, hypertension</td>
<td>Respiratory failure</td>
<td>3</td>
<td>2</td>
<td>1</td>
<td>-</td>
<td>RSV</td>
<td>Survived</td>
</tr>
<tr>
<td>8</td>
<td>50</td>
<td>F/W</td>
<td>Diabetes mellitus, hypertension</td>
<td>Diabetic ketoacidosis, coma</td>
<td>4</td>
<td>3</td>
<td>3</td>
<td>+</td>
<td>NT</td>
<td>Survived</td>
</tr>
</tbody>
</table>

Mean age = 55.2 ± 5.9§

| RSV-Negative |          |           |                   |                       |                  |                      |                     |         |              |                |
|--------------|----------|-----------|-------------------|-----------------------|------------------|----------------------|                     |         |              |                |
| 3            | 27       | F/B       | Schizophrenia     | Drug overdose, seizures, coma, aspiration pneumonia | 12               | 12                   | 5                   | . . .    | Died         |                |
| 6            | 59       | F/B       | None              | Respiratory failure 2° to pneumonia and sepsis (S pneumoniae) | 17(1)            | 15                   | 10                  | . . .    | Died         |                |
| 7            | 56       | F/B       | Myasthenia gravis, paraplegia | Respiratory failure 2° to pneumonia (Staphylococcus aureus) | 20               | 16                   | 5                   | NT      | Survived     |                |
| 9            | 36       | F/W       | AIDS, vaginal cancer | Respiratory failure 2° to pneumonia | 6                | 6                    | 5                   | -       | . . .         | Died           |
| 10           | 43       | M/B       | Diabetes mellitus, hypertension | Respiratory failure 2° to pneumonia (St agalactiae) | 17               | 17                   | 1                   | HSV†    | . . .         | Died           |
| 11           | 66       | F/B       | COPD, IHSS, obesity | Cardiopulmonary arrest | 10(3)            | 10                   | 7                   | -       | . . .         | Survived       |

Mean age = 47.8 ± 15.0§

*W = White; B = black; NT = not tested; CABG = coronary artery bypass graft surgery; 2° = secondary; AIDS = acquired immunodeficiency syndrome; IHSS = idiopathic hypertrophic subaortic stenosis.
†Days hospitalized prior to intubation in parentheses.
§p = 0.33, t-test.

change in CF antibody to influenza A, indicating infection, and patient 6 had an illness titer of 1:64 to influenza B, suggesting recent disease. Chart review yielded no evidence that these three patients had received influenza vaccine.

During the study interval, 48 patients were admitted to the medicine wards with the diagnosis of asthma, pneumonia, or COPD. Four (8.3 percent) of these had respiratory secretions positive for RSV (Table 3). The four RSV-positive patients accounted for 0.5 percent of all medicine ward admissions during the study. These patients tested positively within three days of admission suggesting community acquisition of infection. Only patient 1 had a significant bacterial isolate, Streptococcus pneumoniae, from sputum. No other viral or bacterial isolates were reported in the RSV-positive patients. Patient 4 was receiving immunosuppressive doses of prednisone.

**Discussion**

The hazards of nosocomial RSV infection in pediatric units are well known. The potential threat to hospitalized adults is being scrutinized. The severity of RSV infection is maximal at the extremes of age and throughout life in the immunocompromised or pulmonary impaired. Potential sources of hospital-acquired RSV include infected personnel and/or passive transmission of infected secretions by healthy personnel. The latter route is highly probable, since it has been shown that RSV in secretions from infected
infants may survive on countertops for up to 6 h, on cloth gowns and paper tissue for 30 to 45 min, and on skin as long as 20 min.\textsuperscript{41} The RSV may be recovered from hands contacting any of these contaminated items, and fomite spread of RSV also occurs.\textsuperscript{41,42}

The role of intubation in facilitating nosocomial spread of respiratory viruses has been observed in neonates.\textsuperscript{33} It is postulated that these infants are at greater risk for viral infections because intubation increases the need for frequent airway manipulations which consequently entail lengthier exposures to larger numbers of personnel. In addition, intubation effectively bypasses the upper airway clearance mechanisms, possibly increasing the inoculum to the lungs. The effect of inoculum size on severity of RSV disease has been demonstrated in adult volunteers.\textsuperscript{43} The increased inspired oxygen concentrations usually required by intubated patients are known to alter alveolar macrophage function and diminish tracheal mucus velocity, further attenuating airway defense mechanisms.\textsuperscript{44,46}

The finding of RSV in an intubated adult in the MICU during a community outbreak of RSV led us to screen prospectively for this infection in intubated adults. Forty-five percent of intubated adults in the MICU demonstrated RSV in respiratory secretions.

Patient 4 clearly manifested nosocomial RSV infection as initial screening was negative followed by a confirmatory test on hospital day 18. Patients 1 and 2 presumably represented nosocomial disease due to prolonged hospitalizations prior to testing. Community-acquired RSV disease was diagnosed in patients 5 and 8 as each tested positive for RSV soon after admission.

The lack of specific serum antibody rise in the RSV-positive individuals is not unexpected as many persons do not experience a measurable change with acute infection or, as in the case of most adults, a reinfection.\textsuperscript{1,19} We found the RSV-CF and RSV-IFA serologic studies to be not helpful and contradictory. The CF study revealed no evidence of RSV-specific antibody. The IFA revealed high, unchanging titers in sera obtained during both illness and convalescence. High, unchanging antibody titers to RSV have been observed in adults by other investigators using CF.\textsuperscript{13,16,47} Others, using an RSV-IFA IgG assay, have found that in elderly subjects levels of specific IgG persisted at relatively high levels for months.\textsuperscript{48} We suspect insensitivity of the CF assay and excessive sensitivity of the IFA at our reference laboratories for detection of RSV-specific IgG.

The IFA to detect RSV-specific IgM may prove

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**Table 2—Serologic Findings in Nine MICU Patients and Four MICU Personnel**

<table>
<thead>
<tr>
<th>Patient No. or Employee (age, yr)</th>
<th>RSV (Culture or EIA)</th>
<th>IgG Titer</th>
<th>IgM Result</th>
<th>Other Serologic Diagnoses</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Illness</td>
<td>Convalescence</td>
<td>Illness</td>
</tr>
<tr>
<td>1 (54)</td>
<td>+</td>
<td>1:2,560</td>
<td>NT\textsuperscript{†}</td>
<td>+</td>
</tr>
<tr>
<td>3 (27)</td>
<td>-</td>
<td>1:2,560</td>
<td>NT\textsuperscript{†}</td>
<td>-</td>
</tr>
<tr>
<td>4 (56)</td>
<td>+</td>
<td>1:10,240</td>
<td>1:10,240</td>
<td>-</td>
</tr>
<tr>
<td>5 (64)</td>
<td>+</td>
<td>1:2,560</td>
<td>1:2,560</td>
<td>-</td>
</tr>
<tr>
<td>6 (59)</td>
<td>-</td>
<td>1:2,560</td>
<td>NT\textsuperscript{†}</td>
<td>-</td>
</tr>
<tr>
<td>7 (56)</td>
<td>-</td>
<td>1:10,240</td>
<td>1:10,240</td>
<td>-</td>
</tr>
<tr>
<td>8 (50)</td>
<td>+</td>
<td>1:2,560</td>
<td>NT\textsuperscript{†}</td>
<td>-</td>
</tr>
<tr>
<td>9 (36)</td>
<td>-</td>
<td>1:10,240</td>
<td>1:10,240</td>
<td>-</td>
</tr>
<tr>
<td>10 (43)</td>
<td>-</td>
<td>1:10,240</td>
<td>1:10,240</td>
<td>-</td>
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<tr>
<td>Physician (36)</td>
<td>+</td>
<td>1:10,240</td>
<td>1:10,240</td>
<td>-</td>
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<tr>
<td>Physician (27)</td>
<td>-</td>
<td>1:2,560</td>
<td>1:2,560</td>
<td>-</td>
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<tr>
<td>Nurse (38)</td>
<td>-</td>
<td>1:10,240</td>
<td>1:10,240</td>
<td>-</td>
</tr>
<tr>
<td>Nursing aide (32)</td>
<td>-</td>
<td>1:10,240</td>
<td>1:10,240</td>
<td>-</td>
</tr>
</tbody>
</table>

\*NT = not tested; + = present; - = absent.  
\textsuperscript{†}Died.

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**Table 3—General Medicine Ward Patients with RSV**

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Age, yr\textsuperscript{*}</th>
<th>Sex/Race</th>
<th>Underlying Disease or Risk Factor</th>
<th>Hospital Day Tested/ Days Hospitalized</th>
<th>RSV-EIA</th>
<th>Viral Culture</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>71</td>
<td>M/Black</td>
<td>COPD, hypertension, pneumonia (S pneumoniae)</td>
<td>2/5</td>
<td>+</td>
<td>-</td>
<td>Survived</td>
</tr>
<tr>
<td>2</td>
<td>53</td>
<td>F/Black</td>
<td>COPD, cirrhosis, diabetes mellitus, ethanol abuse, pancreatic cancer, pneumonia</td>
<td>3/3</td>
<td>-</td>
<td>+</td>
<td>Survived</td>
</tr>
<tr>
<td>3</td>
<td>65</td>
<td>M/Black</td>
<td>COPD, diabetes mellitus, nursing home resident</td>
<td>1/5</td>
<td>+</td>
<td>+</td>
<td>Survived</td>
</tr>
<tr>
<td>4</td>
<td>62</td>
<td>M/White</td>
<td>COPD, home oxygen therapy</td>
<td>3/17</td>
<td>-</td>
<td>+</td>
<td>Died</td>
</tr>
</tbody>
</table>

\*Mean age = 62.8 ± 7.5 years.
useful in confirming recent infection in adults, as in patient 1. Investigators using IFA, EIA, and capture EIA have sought an IgM response in elderly patients. The RSV-specific immunoglobulin M was seldom detectable within the first week of illness but 85 percent of patients were found to be positive when tested between days 11 and 30 after onset of disease. Immunoglobulin M persisted for over six weeks in some individuals. The authors concluded that detection of RSV-specific IgM was a useful tool for the diagnosis of RSV in elderly patients, particularly since nasopharyngeal secretions from older adults may be suboptimal for direct antigen testing due to the dry mucosa and viscid mucus characteristic of that age group. Others have found RSV-specific IgM in only 11.5 percent of infected elderly patients peaking after 2 to 6 months.

Dual viral or viral-bacterial infections are being increasingly recognized in adults and children. Patient 2 demonstrated evidence of RSV initially, and late in his illness HSV grew from a tracheal aspirate. Patient 5 had culture-proven RSV infection and a fourfold rise in CF antibody to influenza A. Patient 6 had serologic evidence of influenza B and subsequently was culture-positive for HSV. *Staphylococcus aureus* and influenza A were demonstrated in patient 7. In patient 9, with newly diagnosed acquired immunodeficiency syndrome, *C albicans* and *Cr neoformans* grew from her tracheal aspirate, and HSV grew from a lung biopsy specimen. Isolation of HSV from the respiratory tract of severely ill adults suggests endogenous reactivation or nosocomial inoculation rather than primary infection. Evidence for dual viral-viral or viral-bacterial disease should be sought in any patient experiencing an atypical or unusually severe pulmonary infection, particularly when a specific respiratory pathogen is prevalent in the community.

The observation that 8.3 percent of general medicine ward patients admitted for respiratory disease had evidence of RSV infection is similar to that of Zaroukian and Leader (5.5 percent).10 These patients frequently remain undiagnosed and can serve as a reservoir for nosocomial transmission of infected secretions if appropriate isolation precautions are not utilized.

This investigation was limited by several factors. It would have been desirable to begin screening patients 1 and 2 earlier in their hospitalizations to confirm nosocomial acquisition, as was done in patient 4. In addition, nonintubated MICU patients were not evaluated. A prospective study of all patients admitted to the MICU beginning at the onset of a community outbreak of RSV would define more accurately the incidence of RSV infection in the MICU, the risks associated with nosocomial infection, and the outcome.

In this survey, endotracheal tube aspirates were cultured for viruses and screened for RSV antigen by EIA. Due to lack of personnel, simultaneous nasopharyngeal specimens were not obtained in intubated patients. Studies, primarily of pediatric patients, have shown that nasopharyngeal washes and nasopharyngeal aspirates are superior to nasopharyngeal swabs for detection of RSV by culture56,57 or EIA. Whether the observation that the respiratory mucosa in the elderly is often dry and the mucus viscous, even when infected, indicates that the yield of nasopharyngeal preparations from these patients will be suboptimal is not known. Prior studies have utilized tracheal aspirates in comparing detection of RSV by culture and rapid antigen techniques but yields were not specified by collection method. Clinical studies in immunocompromised patients have shown that RSV culture and/or rapid antigen detection methods are useful when performed on sputum, tracheal aspirates, bronchoalveolar lavage fluid, a sinus aspirate, throat swabs, and lung tissue. Lastly, it must be noted that although RSV outbreaks occur annually, the extent of activity is variable and observations made during a single season may not be applicable to another.

This survey demonstrates that during community outbreaks of RSV infection, some adults admitted to the MICU may already be infected with RSV, and that those admitted for other illnesses may experience nosocomial infection. Likely sources of hospital-acquired RSV include infected personnel and/or transmission of infected secretions by healthy personnel. Prolonged hospital stays and intubation during RSV season may be significant risk factors for nosocomial infection.

Physicians and hospital personnel should be aware of the epidemiology of RSV and the potential hazards of RSV infection in critically ill adults in the MICU. Appropriate infection control precautions must be followed to prevent spread among MICU patients and employees. A prospective series conducted during a number of RSV seasons is required to determine whether acquisition of RSV infection affects morbidity or survival in critically ill patients.

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