

Respiratory Syncytial Virus Infection in Adults

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INTRODUCTION	371
BASIC VIROLOGY	372
Viral Structure	372
Antigenic Characteristics	372
Growth Characteristics	372
Transmission	372
EPIDEMIOLOGY	372
Elderly Adults	372
Long-term care facilities	372
Community-dwelling elderly	374
Adults with Cardiopulmonary Conditions	375
Chronic obstructive pulmonary disease	375
Cardiac disease	375
Asthma	375
Immunocompromised Adults	375
Cancer patients and transplant recipients	375
Human immunodeficiency virus	375
Nosocomial Infections	376
CLINICAL MANIFESTATIONS	376
Young Adults	376
Elderly Adults	376
Immunocompromised Adults	376
PATHOGENESIS	377
IMMUNITY	377
Humoral	377
Cellular	378
DIAGNOSIS	378
Culture	378
Antigen Detection	378
Serology	379
RT-PCR	379
TREATMENT	379
Elderly Patients	379
Immunocompromised Patients	379
PREVENTION	380
Infection Control	380
Vaccination	380
CONCLUSIONS	380
REFERENCES	380

INTRODUCTION

In 1956, a novel virus was recovered from a chimpanzee with respiratory symptoms and designated chimpanzee coryza agent (134). In the ensuing decade, the virus was renamed respiratory syncytial virus (RSV) to reflect the giant syncytia which formed in tissue culture, and epidemiological studies clearly established it as the most important cause of serious respiratory tract infection in infants and young children (19, 135, 149). Although RSV infection was reported in adults with pneumonia in the 1960s, it has only been during the last decade that the

potential for widespread occurrence with serious clinical impact in this population has been recognized (1, 42, 44, 55). Epidemiological studies suggest that the clinical impact of RSV in certain adult populations may approach that of non-pandemic influenza (52, 139). Those who appear to be at increased risk for serious disease include adults with underlying cardiopulmonary disease, frail elderly persons living in long-term care facilities or at home, and the severely immunocompromised (34, 42, 44, 180). Despite growing appreciation of this problem, there are significant gaps in our understanding of RSV infection in adults, especially with regard to immunology, diagnosis, treatment, and prevention. Development of an RSV vaccine for both pediatric and adult immunization offers the best hope to reduce disease burden, although three decades of effort have yet to yield an effective and safe vaccine. This review will discuss the epidemiology, clinical

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TABLE 1. RSV structural proteins in order of gene sequence, 3' to 5'

Protein	Size (kDa)	Designation	Comments
N ^a	44	Nucleocapsid protein	Major target of CTL in humans
P ^a	34	Phosphoprotein	
M	28	Matrix protein	Glycosylated transmembrane protein; no neutralizing epitope known; participates in cell fusion (91)
SH	7.5-30	Small hydrophobic protein	
G	90	Attachment protein	Antigenic variation between strains; neutralizing epitopes; truncated secreted form (Gs) from second open reading frame (158)
F	70	Fusion protein	Sequence conserved between strains; contains neutralizing epitopes
M2-1, M2-2	22	Transcription regulation	Two open reading frame products (ORF1 and ORF2) important for full-length mRNA production by polymerase and transcription regulation (23)
L ^a	~200	Polymerase protein	

^a N, P, and L together constitute the viral replicase.

manifestations, immunology, diagnosis, treatment, and prevention of RSV infection in adults.

BASIC VIROLOGY

Viral Structure

Human RSV is an enveloped RNA virus and is a member of the family *Paramyxoviridae*, classified within the genus *Pneumovirus* (22). The *Paramyxoviridae* include two other genera, *Morbillivirus* (measles virus) and the *Paramyxoviruses* (mumps and parainfluenza viruses). The nonsegmented, single-stranded, negative-sense RNA genome is composed of approximately 15,222 nucleotides and 10 genes which encode 11 proteins (22, 23, 72). The gene order is NS1 (nonstructural 1), NS2, N, P, M, SH, G, F, M2, and L (Table 1). The virus is composed of a nucleocapsid core of N, P, and L proteins (which together is the viral replicase) and virion RNA surrounded by a lipid bilayer obtained from the host cell membrane into which are embedded three transmembrane glycoproteins (G, F, and SH). Infection is initiated with the G protein binding to a host cell receptor, possibly a heparin-like glycosaminoglycan, followed by F protein-mediated fusion of the viral and cell membranes and penetration of the nucleocapsid complex into the cytoplasm (50). Antibodies directed against the F or G glycoprotein neutralize virus in vitro and in vivo.

Antigenic Characteristics

Human RSV isolates can be classified into two major groups, A and B, each containing several distinct subgroup (5, 16, 86, 94, 129). This classification is based upon antigenic and genomic differences found in several viral proteins, but especially the G protein (104, 105, 184). Nucleotide and amino acid sequence homology of the G gene between group A and group B RSV is 67 and 53%, respectively (15, 105, 173). In contrast, the F protein is highly conserved among strains (79% nucleotide and 89% amino acid homology) (22, 104). Consistent with this, the antibody response to primary RSV infection is characterized by cross reactivity with F proteins from group A or B virus, while the response to the G protein is highly group and even subgroup specific (16, 93). Furthermore, immunization of animals with F protein from a group A virus provides resistance to group A and B virus challenge, while immunization with G proteins provides protection only from the homologous strain (171, 172).

Group A and B viruses generally circulate simultaneously within geographically confined epidemics, although group A viruses are more prevalent (4, 86). During a 15-year period in Rochester, New York, group A viruses dominated in 9 years,

group B dominated in 2 years, and the distribution was nearly equal in four seasons (86). The dynamics of annual epidemics appear to be local rather than national or global (4). In nosocomial outbreaks in a nursing home and a bone marrow transplant unit, both group A and B viruses were identified, indicating independent introduction and spread of several distinct viruses (30, 44). Some studies have found that disease severity in infants is more severe with group A RSV infection than with group B infection, but this relationship has not been evaluated in adults (126, 182).

Growth Characteristics

RSV has important characteristics that can make it difficult to propagate in cell culture. Although the virus grows in a variety of cell lines, including HEp-2, HeLa, and Vero cells, the typical syncytial cytopathic effect and viral titer vary considerably depending upon the virus strain and the condition of the cells (181). Titers of $>10^7$ PFU/ml are difficult to obtain with many strains. RSV is thermolabile and rapidly loses titer at room temperature (32, 181). Typical of enveloped viruses, RSV is readily inactivated by detergents.

Transmission

RSV is shed in high titers from infants hospitalized for lower respiratory tract disease for up to 21 days (78). Shedding during natural RSV infection in adults has been most closely studied in hospital personnel, who are generally young, healthy adults, and averages 3 to 6 days, with a range of 1 to 12 days (82, 87). In adult challenge studies, volunteers excrete virus for approximately 4 to 5 days (range, 1 to 8 days) (85, 130). Shedding of virus in older adults has not been specifically studied but is presumed to be relatively low titer and of short duration, since diagnosis by viral culture is difficult (43). RSV is believed to be spread primarily by large droplets and fomites and can survive on nonporous surfaces, skin, and gloves for many hours (77, 79). Thus, close person-to-person contact or contact with contaminated environmental surfaces and autoinoculation are required for transmission. Small-particle aerosols are not considered a major mode of spread, since the virus is not stable when aerosolized (157).

EPIDEMIOLOGY

Elderly Adults

Long-term care facilities. Although RSV infection was reported in 18 hospitalized older adults in Sweden as early as 1967, it was not until several nursing home outbreaks were

TABLE 2. Reports of RSV infections in LTCF

Study ^a (reference)	Yr	Study method	No. of RSV cases	Attack rate (%)	Method of diagnosis ^b	Pneumonia (% of cases)	Death (% of cases)	Comment
Hornsleth et al. (100)	1975	Prospective	10	7	CF*	0	0	Most asymptomatic
CDC (18)	1977	Outbreak	15	19	CF	47	40	Several employees ill
Garvie and Gray (60)	1980	Outbreak	40	43	CF		3	
Mathur et al. (123)	1980	Prospective	8	1.4	Culture, CF	25	0	Concurrent influenza A outbreak
BCDSC ^c (155)	1983	Outbreak	15	NA ^d	Culture, CF		53	
		Outbreak	24	89	Culture, CF		10	
		Outbreak	16	40	CF		0	
Morales et al. (133)	1983	Prospective	12	10	Culture, CF	16	5	All RSV cases had lower respiratory tract disease
Hart (90)	1984	Outbreak	20	40	Culture, CF		20	Steady trickle of cases
Sorvillo et al. (165)	1984	Outbreak	40	40	Culture, CF	55	20	High rate of radiographic pneumonia
Mandal et al. (120)	1985	Outbreak	8	30	CF	13	13	
Arroyo et al. (8)	1988	Prospective	5	9	CF*	0	0	
Gross et al. (73)	1988	Prospective	8	3.4	CF*		0	Concurrent influenza outbreak
Agius et al. (1)	1990	Outbreak	52	12	CF, IFA, WB	42	12	Pharyngitis, gastrointestinal complaints uncommon
Nicholson et al. (140)	1990	Prospective	9	2	Culture, CF		0	
Falsey et al. ^c (39)	1990	Prospective	2	2.3	EIA*			Marked difference in attack rates at two local nursing homes
		Prospective	11	18	EIA*			
Osterweil and Norman (148)	1990	Prospective	34	15	CF	3	2	
Falsey et al. (44)	1992	Prospective	40	7	Culture, EIA*	10	5	Clear clustering on floors
Wald et al. (179)	1995	Prospective	9	3.5	Culture	22	0	Gastrointestinal symptoms uncommon
Orr et al. (147)	1996	Prospective	3	2	CF	33		Only evaluated febrile illnesses

^a CDC, Centers for Disease Control; BCDSC, British Communicable Diseases Surveillance Centre.

^b CF, complement fixation serology; greater than fourfold rise or single high-titer convalescent-phase sample considered diagnostic; WB, Western blot; *, greater than fourfold rise in titer required for diagnosis.

^c More than one outbreak reported in a single publication.

^d NA, not available.

described in the late 1970s and early 1980s that RSV was appreciated as a serious pathogen in the elderly (18, 55, 60, 123). Since that time, there have been seven reports of outbreaks and 11 prospective studies in long-term care facilities (LTCF) in which RSV was identified (Table 2) (1, 8, 18, 39, 44, 60, 73, 90, 100, 120, 123, 133, 140, 147, 148, 155, 165, 179). Attack rates range widely, from 1 to 89%, and may depend upon the case definitions and diagnostic tests used. Prospective studies in which all respiratory infections were evaluated and RSV cases were defined as a positive culture or a greater than fourfold rise in antibody probably reflect the most accurate RSV infection rates. In these studies, rates of infection ranged from 2 to 12% (1, 8, 44, 100, 140). Infection rates in institutionalized persons may also be variable because the outbreaks occur in closed populations and the virus is subject to nosocomial spread. During one season in Rochester, New York, two nursing homes were assessed for influenza and RSV; at one institution, influenza A was prevalent and RSV accounted for only 3% of illnesses, whereas at the other home, RSV was the dominant pathogen and caused 20% of the illnesses (39).

Complication rates in previous reports have also been quite variable, with the incidence of pneumonia ranging between 0 and 55% and death rates of 0 to 53% (100, 155, 165). Again, these marked differences in severity may be due in part to case definitions used in outbreak situations, but there may also be differences in strain virulence or the chronic medical conditions of residents. For example, in the report by Sorvillo, the attack rate for symptomatic RSV illness was high at 40%, and 55% of those ill had radiographically documented pneumonia (165). This is in contrast to the study by Osterweil, in which

pneumonia and death rates were 5 and 2%, respectively (148). The true incidence of pneumonia in residents of LTCF may be underestimated because chest radiographs are not routinely obtained. Although rates of documented pneumonia can be variable, lower respiratory signs are common in most studies of RSV (44, 60, 140).

Elderly persons who attend senior daycare programs also appear to be at increased risk for RSV infection. One study, which examined viral infections among staff and elderly participants of a daycare program, found RSV to be a common pathogen in both groups (37). Over a 15-month period, 10% of 165 elderly and 5% of the 113 staff members developed respiratory infections caused by RSV. This agent was among the most commonly identified viruses, along with influenza A virus and coronaviruses. Of interest, children from a nearby center visited with elderly participants approximately once a week, although transmission of viruses was not evaluated specifically.

Although most of the current information on RSV in institutionalized persons involves elderly persons, there is one report of an RSV outbreak in a residential institution for mentally retarded young adults (51). The attack rate was 50% and substantial morbidity was associated with illness. Of the 24 affected individuals, 42% wheezed, 17% were hospitalized, and a 19-year-old woman with multiple medical problems died. Both younger age and less time institutionalized were risk factors for infection with RSV.

In summary, RSV appears to be a predictable cause of wintertime respiratory illnesses in LTCF. Although rates vary from year to year and with individual institutions surveyed, a reasonable estimate is that RSV will infect 5 to 10% of resi-

TABLE 3. RSV pneumonia in adults

Study (reference)	Location, dates	Diagnostic test(s) ^a	No. positive/no. tested (% positive)
Fransen et al. (54)	Sweden, 1963–66	CF	31/598 (5.2)
Hers et al. (96)	Netherlands, 1967–68	CF	10/207 (4.3)
Vikerfors et al. (178)	Sweden, 1971–80	CF, Ag, IgM	57/2,400 (2.0)
Kimball et al. (109)	USA, 1980–81 ^b	Culture, CF	2/100 (2.0)
Stanek and Heinz (169)	Czechoslovakia, 1983–85	Culture, CF	2/74 (2.7)
Zaroukian and Leader (194)	USA, 1987–88 ^b	IAH, Ag, culture	3/55 (5.4)
Melbye et al. (128)	Norway, 1988–89 ^b	CF	5/36 (13.9)
Falsey et al. (42)	USA, 1989–92 ^b	Culture, Ag, EIA	69/483 (14.3)
Marrie (121)	Canada, 1991–94	CF	0/149 (0)
Dowell (27)	USA, 1990–92	EIA	53/1,195 (4.4)
Ruiz et al. (159)	Spain, 1996–97	Serology not specified	5/204 (2.4)

^a CF, complement fixation; Ag, antigen; IAH, immune adherence hemagglutination.

^b Winter seasons only evaluated.

dents per year, with rates of pneumonia and death of 10 to 20% and 2 to 5%, respectively.

Community-dwelling elderly. The incidence and impact of RSV infection in older persons who live independently in the community have not been well studied. RSV is thought to be an underrecognized pathogen in older adults, based on case reports of RSV pneumonia, studies of adults with respiratory disease requiring hospitalization, and epidemiological studies from the United Kingdom. A review of RSV isolates in Scotland between 1971 and 1979 indicated that 4 to 18% occurred in adults ages 25 to 29 and 3 to 16% occurred in persons over age 60 (7). An analysis of excess deaths and respiratory disease in England by Fleming and Cross showed that peaks of excess morbidity and mortality in persons over age 65 occurred when RSV activity was highest in the community, as judged from viral isolates recovered from children (52). In most years, the peak of influenza activity occurred simultaneously with RSV, obscuring its effect. However, when the peaks in viral activity were temporally separated, the effect of RSV on excess morbidity and mortality was similar to that seen with influenza. In another analysis of the impact of influenza and RSV in the United Kingdom, Nicholson applied statistical modeling to 15 years of data and estimated that the impact of RSV was greater than that of influenza (139).

In addition to the epidemiological evidence that RSV is a problem in adults, there are a number of reports of adults hospitalized with pneumonia. Many of the case reports involve adults with chronic medical conditions such as Wegener's granulomatosis, systemic lupus erythematosus, and renal failure (136, 167, 193). However, some reports describe previously healthy adults whose only risk factor appeared to be advanced age (114, 193). In one well-documented case, a 72-year-old woman living independently at home with no chronic cardiopulmonary or immunosuppressive diseases died of RSV pneumonia (114).

The earliest large study which specifically sought RSV as a cause of lower respiratory tract disease in community-dwelling adults was performed by Fransen in Sweden from 1963 to 1966 (55). Eighteen persons over age 55 with RSV were identified, and the highest rate of RSV infection was found in the ≥60-year-old group, in which 16 of 216 (7.4%) illnesses were due to RSV. In another Swedish study, RSV infections were identified serologically in 57 adult patients over a 10-year period (178). The median age was 75 years, and the incidence of pneumonia was 63%. In two other studies which used viral culture alone for diagnosis, RSV was detected in 2 to 5% of patient samples (109, 194). Two more recent, larger studies of hospitalized

adults again show RSV to be a common pathogen (27, 42). In a study of elderly persons in upstate New York admitted during three winters with acute cardiopulmonary conditions, RSV was identified in 10% of patients, compared to 13% with influenza (42). The morbidity was substantial, with 18% of patients admitted to intensive care and 10% requiring ventilatory support, and 10% died. Although 44% had a discharge diagnosis of pneumonia, much of the RSV morbidity was associated with other diagnoses, including chronic obstructive pulmonary disease (COPD) exacerbation (19%) and congestive heart failure (20%). A recent study by Dowell et al., which was not limited to elderly adults, found RSV to be the third most common identifiable cause of pneumonia at 4.4% in 1,195 adults with community-acquired pneumonia (27). This compared to *Streptococcus pneumoniae* at 6.2% and influenza virus at 5.4%. Of the 57 RSV-infected patients, 32% were younger than 65 and 8 individuals were less than 40 years old. Surprisingly, the young adults were otherwise healthy. Lastly, a number of studies evaluating the etiology of community-acquired pneumonia have identified RSV with variable success (Table 3) (27, 42, 54, 96, 121, 128, 159, 169, 178, 194). The variability in infection rates likely reflects the diagnostic tools used and seasons studied but may also reflect some differences in geographic distribution of the virus. A reasonable estimate using data from a number of studies during the past 30 years is that RSV accounts for 2 to 5% of pneumonias throughout the year and 5 to 15% during the winter.

Prospective studies, which evaluate the total burden of RSV disease in community-dwelling older persons, have yet to be done. A number of large surveillance studies of acute respiratory infection (ARI) show declining rates of infection with advancing age, yet the number of middle-aged and older adults studied was small (132). Hodder et al. evaluated the rates of ARI but not specific pathogens in noninstitutionalized adults over age 65 (99). The average incidence of ARI was 2.5 per 100 person-months and was significantly greater for those living in congregate settings (3.2) and those regularly caring for young children (3.0). Nicholson conducted the only prospective study of ARI in elderly persons in the community to date, which examined the frequency of specific viral pathogens (141). RSV accounted for 3% of the 497 illnesses among 533 persons followed for two winter seasons. This compared to 7% identified as influenza and 52% due to rhinoviruses. A true comparison of the burden of disease from specific pathogens is not possible because very different diagnostic tools were used for each pathogen.

Adults with Cardiopulmonary Conditions

Chronic obstructive pulmonary disease. As with influenza, adults with underlying heart and lung conditions appear to be at high risk for severe RSV infections (27, 42). Infection is felt to be a common cause of exacerbations of COPD, although comprehensive studies which employ sensitive viral diagnostic tests are lacking (14, 36). Most of the published series to date have been small, and the percentage of illnesses caused by RSV in persons with COPD ranges widely, from 0 to 17.4% (14, 17, 36, 75, 112, 113, 162, 164, 170, 180, 192). In 1963, Carilli studied 30 subjects between the ages of 26 and 80 years who met the criteria for chronic bronchitis (17). RSV was the most commonly identified pathogen and was associated with 8 of 46 (17%) illnesses. During the same year, Sommerville, in Glasgow, Scotland, also found RSV to be a common pathogen in a retrospective study of persons with an exacerbation of chronic bronchitis. Of the 96 subjects showing a rise in RSV antibodies, 85% were over age 21, and half of the adult RSV cases were diagnosed with exacerbation of chronic bronchitis (164). In contrast, Smith and colleagues evaluated more than 1,000 exacerbations of COPD over a 6-year period in 150 subjects and found only 16 RSV infections, of which only 50% were associated with illness (162). A recent 2-year study of 134 community-dwelling adults with cardiopulmonary disease documented eight RSV infections (4.3 per 100 subject winters). The illnesses were associated with significant morbidity, as three of the eight were hospitalized with wheezing and worsening hypoxia (180). Unexpectedly, regular contact with children did not appear to be a risk factor for infection in this small study.

Cardiac disease. Although less information is available, chronic cardiac disease is also believed to be a risk factor for severe RSV disease. Sixty-three percent of individuals hospitalized with RSV in a study from Rochester, New York, had underlying cardiac disease (42). In the previously mentioned study of 134 cardiopulmonary patients, 46 had congestive heart failure as their primary diagnosis. Viral infections were diagnosed in 23% of the acute cardiopulmonary illnesses and were twice as common in the cardiac patients as in the COPD group. It was postulated that the frail cardiac patients may have been more mobile and thus more likely to be exposed to the virus than their pulmonary disease counterparts, who were commonly on oxygen at home. Much of the increased morbidity and mortality associated with influenza is due to atherosclerotic vascular events following infection (62). Whether RSV is associated with similar effects is unknown, but a recent study looking for viral antigens in the lung tissue from 20 persons dying of myocardial infarction found influenza A virus and RSV antigens in one person each (152).

Asthma. A number of studies of children from birth to adolescence have indicated that RSV is one of the most common precipitants of infection-induced wheezing (116, 163, 186). In addition, there is some evidence that severe RSV bronchiolitis early in life may be a risk factor for asthma in later life (98). The association of viral infections and asthma exacerbations in adults is less well defined. The results of several studies indicate that viral infections which appear clinically to be restricted to the upper airway may be associated with bronchial hyperactivity and small-airway dysfunction (29, 116, 151). Hall et al. demonstrated abnormalities of lung function, including elevated total respiratory resistance and exaggerated responses to carbachol challenge, for up to 8 weeks following RSV infection in normal, healthy adults (87). In addition, a recent study of Norwegian adults found that increasing RSV complement-fixing antibody titers were related to progressively worse lung

function (144). The presence of RSV antibodies was an independent predictor of reduced 1-s forced expiratory volume in approximately 1,200 adults aged 18 to 73 years even after subjects with recent respiratory symptoms were excluded.

The rates of documented viral infections in adults with asthma have ranged from 0 to 44% in different prospective studies (12, 21, 101, 142, 163). Hudgel and coworkers diagnosed viral infections in 11% of wheezing episodes, of which RSV accounted for one of eight viruses identified (101). Beasley and colleagues found 10% of 178 asthma exacerbations in 31 adults to be associated with viruses (12). Of note, 14 of the 30 viruses identified in asthmatics were RSV; 89% of those cases were associated with wheezing and 38% were judged to be severe. The low rates of documented viral infections in some asthma studies, despite high frequencies of upper respiratory infection symptoms, may reflect the insensitivity of current viral diagnostic tests.

In summary, RSV infection has been documented as a cause of serious disease in a number of adult populations which include the elderly and adults with chronic heart and lung diseases. In addition to the suffering, the economic burden of RSV in older adults in the United States is estimated to be \$150 to \$160 million annually for pneumonia alone and is likely much higher if exacerbations of chronic conditions such as congestive heart failure and emphysema are included (88).

Immunocompromised Adults

Cancer patients and transplant recipients. The first comprehensive report of RSV infection in the immunocompromised host was published by Hall et al. in 1986 and described the clinical course of 47 children who were compromised by virtue of chemotherapy, steroids, or congenital immunodeficiency (83). Since 1986, numerous studies have shown RSV to be a cause of serious disease in immunocompromised adults as well (13, 25, 26, 34, 53, 89, 97, 136, 160, 161, 187, 189–191). These studies include a variety of conditions such as leukemia, bone marrow transplantation (BMT), and solid organ transplants. RSV infections occur in immunocompromised persons when RSV is prevalent in the community (25, 191). In a 3-year period at the M. D. Anderson Hospital, 181 respiratory viruses were isolated in 668 illness episodes. The most commonly identified virus was RSV, accounting for 31% of isolates, followed by picornaviruses (28%) and influenza viruses (18%). The high percentage of RSV is unusual in adults but was also noted in a study of BMT patients, in whom RSV accounted for 49% of 67 viral isolates, and in 10% of respiratory infections in leukemic patients (189–191). Although infection may occur in the community, nosocomial infection is common, accounting for 30 to 50% of the cases (34, 53, 189–191). It is presumed that virus is introduced by ill visitors or staff members, and in the outbreak in BMT patients reported by Harrington et al., RSV was detected in 35 of 435 employees and family members (89). Of these, 82% had symptomatic upper respiratory tract infections.

RSV infection in the immunocompromised host is associated with significant morbidity and mortality, particularly BMT patients prior to marrow engraftment. In this group, rates of pneumonia may be as high as 80%, with death rates of 70 to 80% in those who develop pneumonia (34, 189, 191). Recipients of solid organ transplants and BMT patients postengraftment appear to have a better prognosis (34, 191).

Human immunodeficiency virus. In general, the clinical presentation of RSV in human immunodeficiency virus (HIV)-infected persons is similar to its presentation in individuals without HIV infection, although occasional severe disease has

been described (110). Prolonged viral shedding has been documented in children (up to 90 days), but similar data are not available for adults. Two nonfatal cases of RSV pneumonia in HIV-infected adults have been reported (138, 168).

Nosocomial Infections

Nosocomial RSV infections have been clearly demonstrated on pediatric wards and in nurseries since the 1970s but more recently have also been shown to be a problem in adult patients in the hospital and LTCF (80). Outbreaks of RSV have also been documented in adult medical wards, medical and surgical intensive care units, oncology wards, and BMT units (34, 49, 53, 74, 174, 189, 190). Because of the high morbidity and mortality associated with RSV in cancer patients, this problem has been the focus of significant attention (59). However, nosocomial spread of RSV in other groups of adult patients is likely underrecognized. Takimoto described 11 patients with RSV on an adult medical ward during one winter season (174). Two of these patients, both of whom developed pneumonia, had onset of symptoms 7 days after admission. Guidry reported RSV infections among intubated patients in a medical intensive care unit between the months of January and March (74). Five of 11 persons tested were positive for RSV, of whom three had unequivocally acquired RSV in the hospital. A physician who also had symptomatic RSV infection was considered a possible source. Lastly, an outbreak of RSV infections has been reported in a cardiothoracic intensive care unit in which 21 of 46 adults sampled had positive RSV antigen tests during a community outbreak (49). The mean time after admission to diagnosis was 11.5 days (range, 2 to 180 days), and 40% occurred after cardiac surgery. All patients had fever and abnormal chest X-rays, seven had prolonged respiratory failure, and four died. With these few but compelling reports, it seems likely that RSV is present on adult wards much more frequently than is recognized.

CLINICAL MANIFESTATIONS

Young Adults

Reinfection with RSV is common throughout adult life and is generally limited to the upper respiratory tract (81). Early studies in healthy young adults, using both experimental challenge and observation of natural infection, indicated that infections produced only very mild upper respiratory tract symptoms (84, 103, 111, 130). However, a study of 10 healthy hospital staff with natural RSV infections demonstrated more significant symptoms, although none had serious complications (87). All had nasal congestion, fever, and an irritating nonproductive cough, and 8 of 10 missed work for an average of 6 days. Two subjects had transient wheezing, and all had persistent fatigue and intermittent shortness of breath at 4 weeks postillness. Exaggerated airway reactivity was demonstrated on pulmonary function tests for up to 8 weeks.

Elderly Adults

The clinical manifestations of RSV infection in the older adult are quite variable, with symptoms ranging from a mild cold to severe respiratory distress (44). The full spectrum of disease is best seen in prospective studies in LTCF or senior daycare, where all respiratory complaints were evaluated, including minor illnesses (Table 4) (37, 44, 179). It should be noted that these studies involved frail elderly persons with many chronic medical conditions and that the clinical features of RSV in healthy older persons have not been fully elucidated.

TABLE 4. Clinical manifestations of RSV infections in frail elderly persons^a

Indication	% of patients
Symptoms	
Rhinorrhea/nasal congestion.....	67-92
Sore throat.....	20-33
Headache.....	3
Hoarseness.....	22-27
Cough.....	90-97
Sputum.....	22-67
Dyspnea.....	11-20
Systemic/constitutional.....	44-80
Gastrointestinal.....	0
Signs	
Fever >38°C.....	20-56
Rales.....	33-40
Wheezing.....	6-35
Laboratory findings	
Chest X-ray infiltrates.....	0-22

^a Data are from references 27, 37, 42, 44, and 179.

The manifestations of RSV may be difficult to distinguish from those influenza virus or other respiratory viruses; however, there are a few helpful clues which suggest RSV. The typical RSV illness begins with nasal congestion and discharge, and these symptoms help distinguish RSV from influenza (123). Cough is very common and affects 90 to 97% of patients. Fever is seen in approximately 50% of infected persons, compared to 75% with influenza virus or bacterial infections (27, 42). Although temperatures of 39 to 40°C are occasionally seen, fevers are typically lower than in influenza (42, 55). Lower respiratory tract involvement is common, with 30 to 40% of patients having rales and wheezing on examination of the chest (27, 42, 44). The presence of wheezing by report or on exam is another feature which helps differentiate RSV from other infections. In a study by Dowell et al., seven of eight patients between the ages of 18 and 39 with RSV pneumonia presented with wheezing, and none had a history of asthma or lung disease (27). Constitutional symptoms, such as myalgias and malaise, are more common in influenza than RSV infection, as are gastrointestinal complaints (179).

Pneumonia may develop in up to 10% of infected patients (42). Chest radiographs generally do not distinguish RSV pneumonia from bacterial infection and most commonly demonstrate bilateral alveolar opacities but may also show interstitial changes (165). Forty percent of patients in Dowell's study showed consolidation on chest films, with 35% described as lobar (27). The role of bacterial infection with RSV has not been well studied. Pathogens such as *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Staphylococcus aureus* have been demonstrated in up to 30% of cases (42, 133, 178, 194). Since the adequacy of specimens was not addressed, the significance of these findings is uncertain. RSV has occasionally been reported in association with syndromes other than respiratory illness, such as cardiac arrhythmia and neurological disorders, although a definitive causal relationship has not been proven (61, 175).

Immunocompromised Adults

The clinical progression of RSV infection in immunocompromised adults appears to follow a similar pattern as in immunocompetent hosts with upper respiratory infection preceding lower respiratory tract disease and acute lung injury (97). In the report by Harrington and colleagues, 83% of patients

TABLE 5. Clinical signs and symptoms of RSV in immunocompromised adults^a

Indication	% of patients
Symptoms	
Rhinorrhea/sinus congestion.....	61–82
Sore throat.....	11–27
Otalgia.....	36
Nausea/abdominal pain.....	36
Cough.....	87–100
Dyspnea.....	36–45
Signs	
Fever >38°C.....	65–100
Wheezing.....	35–56
Rales/rhonchi.....	50–100
Laboratory findings	
Chest X-ray infiltrates.....	58–75
Sinusitis—X-ray.....	45–75

^a Data are from references 34, 89, 97, and 190.

who developed RSV pneumonia had upper respiratory symptoms ≥ 2 days before pneumonia developed (89). Rhinorrhea, sinus congestion, and otalgia were common complaints (Table 5) and are important clinical features in transplant patients, since they do not occur with cytomegalovirus pneumonia (34, 53, 97, 190). Clinical or radiographic sinusitis appears to be a particularly helpful clue to RSV in the compromised adult, since it may be present even in patients without upper respiratory symptoms (34, 97). Cough, which is most commonly nonproductive, is seen in most patients (87 to 100%), and dyspnea is seen in 36 to 45% (34, 89, 97, 190). Chest radiographs are frequently abnormal, with infiltrates found in 58 to 75%. The usual pattern is bilateral interstitial infiltrates which become increasingly alveolar, with lobar involvement with time (34, 97). Pleural effusions may occur in 17 to 25% of cases (34, 89).

Although RSV infection in the immunocompromised adult is associated with significant morbidity and mortality, the severity of clinical manifestations depends on the magnitude of the immunosuppression. In leukemic patients with severe chemotherapy-induced myelosuppression, 75% of infections were complicated by pneumonia, with a mortality rate of 83% (190). Recipients of solid organ transplants generally are not as ill as persons with hematologic malignancies, but again, the severity of RSV depends on the level of immunosuppression (34). The group at highest risk for severe RSV infection is BMT recipients (34, 53, 97). Those infected preengraftment are at highest risk for pneumonia and death (89, 97). In Harrington's report, 79% of preengraftment patients developed pneumonia, compared with 41% postengraftment (89). In another report of 46 adult BMT patients with documented RSV, the risk of pneumonia and death was closely related to time after transplant (191). In this study, 70% of persons less than 1 month post-transplant developed pneumonia, with a 63% mortality. Pneumonia rates fell to 50% between 1 and 2 months and declined to 24% by 2 months after transplant. Although postengraftment RSV infection less frequently progresses to pneumonia, mortality remains high at 50 to 70% if pneumonia develops (89, 191). Histopathology from autopsied cases shows diffuse alveolar damage and, in some cases, severe squamous metaplasia (89, 97). Multinucleated giant cells and intracytoplasmic viral inclusion are seen in RSV pneumonia, and up to 80% of cells may show RSV antigens on immunofluorescence staining (97, 190).

PATHOGENESIS

The pathogenesis of severe RSV disease in older adults has not been well studied. Lower respiratory tract disease in infants, which is manifested as bronchiolitis and pneumonia, is believed to be due to a combination of small airways and waning maternal immunity (82). In addition, immunologic mechanisms such as production of inflammatory cytokines may contribute to the pathogenesis of disease in babies with bronchiolitis (2). Giant-cell pneumonia with abundant viral inclusions has been described in immunosuppressed children and adults dying from overwhelming RSV infection; however, the mechanisms which make the elderly at risk for severe disease are not known (89, 131). It is presumed that the presence of underlying heart and lung disease, a declining immune system, and an aging respiratory tract may all play a role. Very little is available in the way of pathologic specimens from immunocompetent elderly persons dying of RSV complications with the exception of one case of giant-cell pneumonia that was documented at autopsy (114). However, not all severe RSV infections in the elderly may be due to unchecked viral replication. The high frequency of wheezing in this group also raises the possibility of immune-mediated pathogenesis.

IMMUNITY

Humoral

Despite the frequency of reinfection throughout life, several lines of evidence suggest that at least partial immunity can be induced. Experimental animal data have elucidated the relative importance of humoral, mucosal, and cellular immune mechanisms in protection, recovery from, and immunopathogenesis of RSV disease (66, 67, 146, 183). However, it is not clear that the immune response demonstrated in animal models can be correlated directly to human infection. Among reports correlating serum antibody levels to protection in infants, perhaps the most compelling is the protective effect provided high-risk infants by passively administered immunoglobulin (63, 64, 71, 92, 107, 119, 143). The influence of humoral and mucosal antibody on susceptibility to RSV infection in adults has been evaluated in adult challenge studies using wild-type virus or attenuated vaccine candidates (57, 85, 127, 130, 154, 185). Using a wild-type A2 strain, Mills found that most volunteers shed virus after challenge, although those with low prechallenge nasal neutralizing antibody levels shed large amounts of virus and were more likely to develop upper respiratory illness and to have serum antibody responses than those with high levels of antibody (130). Although they observed a significant correlation between serum and nasal wash neutralizing antibody titers, the relationship between serum antibody and the above clinical findings did not reach statistical significance. Similar findings were reported by Watt using a wild-type group A virus and a temperature-sensitive mutant as the challenge viruses (185). This study was difficult to interpret, however, since few subjects shed virus despite developing serum antibody responses and clinical illness. In another study using A2 wild-type virus, Hall repeatedly challenged 15 young adults who had recently recovered from natural RSV infection (85). There was a statistically significant inverse correlation between rates of infection (defined as virus shedding or four-fold serum antibody response) and prechallenge levels of F, G, and neutralizing antibody in serum. Nevertheless, 25% of subjects with the highest antibody levels could still be reinfected. The same study also noted a trend toward a protective effect of nasal antibody. In contrast to the above reports, neither Fried-

wald nor Pringle noted a relationship between prechallenge serum neutralizing titers and virus shedding after challenge with attenuated viruses (57, 154).

There are few published data on the relationship between serum antibody and susceptibility to natural infection with RSV in elderly adults, and there are no data regarding mucosal antibody. In an analysis of RSV infections in nursing home residents, serum F, G, and neutralizing antibody titers in acute-illness specimens were similar in RSV-infected persons and those with non-RSV illnesses (38). Although there was a trend toward greater illness severity in those with the lowest neutralizing antibody titers, it did not reach statistical significance. This study was not ideal, since the sera analyzed were obtained after subjects were ill and antibody levels may have already started to rise. In a case-control analysis of RSV infections in frail elderly persons attending an adult daycare center, using preillness blood, the mean serum immunoglobulin G (IgG) titers to the F protein and neutralizing titers to group A and B RSV were significantly lower in 22 infected subjects than in matched controls (47). When the 44 cases and controls were combined, 8 of 11 (73%) with antibody levels in the lowest quartile were infected, while only 2 of 11 (18%) with titers in the highest quartile were infected. These results suggest that, among frail elderly subjects, those with low levels of serum antibody may be at greater risk of developing symptomatic RSV infection than those with high antibody titers.

Among the possible reasons for a greater risk of severe illness with RSV in the elderly is waning or impaired immunity to the virus. However, in an analysis of baseline serum F and neutralizing antibody titers, there were no significant differences among young adults, healthy elderly (≥ 60 years), and frail elderly (≥ 65 years) (48). Furthermore, analysis of antibody responses to natural RSV infection found no difference in the magnitude of neutralizing responses and noted a twofold-greater F-specific response in the frail elderly compared to young adults (48). There may have been greater production of nonneutralizing F antibody in the elderly groups following infection, but this observation must be confirmed. There is no information regarding humoral or mucosal immunity in severely immunocompromised individuals.

Cellular

The importance of cellular immunity in clearing RSV has been convincingly demonstrated in animal models (66–68, 145). In the murine model, RSV induces a Th-1 type CD4 response characterized by production of Th-1 cytokines (gamma interferon and interleukin-2 [IL-2] and IL-12) and cytotoxic T cells (CTL) (9, 11, 67, 68, 137, 150). In contrast, immunization with inactivated virus or subunit viral proteins induces a Th-2 type CD4 response with the corresponding cytokines (IL-4, IL-5, and IL-6) and no CTL (3, 68). However, there are few data on the cellular immune response to RSV in either infants or adults (10, 11, 20, 102). Cherrie found that nine of nine young adults had detectable CTL activity in peripheral blood mononuclear cells which recognized the N, SH, M, M2, and NS2 proteins, with N being the dominant target (20). Consistent with these data and the results from animal studies, Anderson found that peripheral blood mononuclear cells from three young adults had RSV-specific increases in Th-1 cytokine mRNA but not Th-2 cytokine mRNA (6).

The importance of CTL activity to either protection or recovery from RSV infection has not been investigated in humans. Furthermore, there are no studies linking cellular immune responses or cytokine production to immunopathogenesis of RSV disease in the adult, as has been clearly

demonstrated in animal models (145). Age-related decline in cellular immunity, specifically CTL, to influenza viruses has been found by several investigators, and it has been suggested that this decline may predispose them to more severe infection (124, 153). However, there are no published reports comparing cellular responses, either CTL or cytokine production, in young adults to those in healthy or frail elderly persons.

DIAGNOSIS

The four principal methods of diagnosing RSV infection in adults are culture, antigen detection by immunofluorescence assay (IFA) or enzyme immunoassay (EIA), RNA detection by reverse transcription-PCR (RT-PCR), and serologically by demonstrating RSV-specific IgM acutely or by a significant rise in RSV-specific IgG antibodies between acute- and convalescent-phase sera. The latter method provides only a retrospective diagnosis.

Culture

Culture, the definitive standard upon which all other methods are judged, is highly sensitive and specific in infants (76). Since adults shed considerably less virus than infants ($\leq 10^3$ versus $\leq 10^6$ PFU/ml) and for a shorter duration (approximately 3 to 4 days), culture would not be expected to be as sensitive in this population (32, 80, 81). The thermolability of RSV compounds the difficulty with culture, and most investigators have relied upon serology for diagnosis in adults (27, 42, 44). In one nursing home study, culture identified 45% of RSV illnesses when a highly sensitive serologic assay was used as the measure of infection (44). It should be noted that optimal culture technique and transport times of under 1 hour were used. Surveillance cultures in an adult daycare center over three winters detected only one-third of 50 serologically confirmed RSV infections among both young staff members and elderly participants (Falsey, unpublished data). In the only published analysis of various diagnostic methods in the elderly, 67% of serologically confirmed RSV illnesses were culture positive when tissue culture inoculation was performed at the bedside and dropped to 45% when specimens were transported to the lab (43).

Antigen Detection

Detection of RSV antigens in respiratory secretions by IFA or EIA, methods with 75 to 95% sensitivity in infants, are even less useful than culture in elderly adults (108). In one analysis of 11 serologically confirmed infections in elderly persons, six of whom were culture positive, only one was positive by IFA and none were positive by EIA (43). In contrast, another investigator reported four EIA-positive and one culture-positive infection among 11 patients tested in a medical intensive care unit outbreak (74).

In the immunocompromised patient, rapid diagnosis is critically important because early therapy may be lifesaving. However, even in cases with extensive pulmonary involvement, diagnostic methods are considerably less sensitive than in infants. Englund reported that the sensitivity of antigen detection using EIA on respiratory secretions was highly dependent upon the type of specimen tested (32). In an analysis of 56 culture-positive patients, nasal wash specimens were positive by EIA in 6 of 40 (15%) samples, endotracheal secretions were positive in 5 of 7 (71%) samples, and bronchioalveolar washes were positive in 8 of 9 (89%) samples. The low yield is probably because virus titers in these specimens were low at 35 and 714 PFU/ml in nasal wash and lower respiratory secretions, respec-

tively. This is in contrast to infants, who often secrete 10^6 PFU/ml in nasal secretions.

Serology

Various serological methods, including complement fixation and EIA, have been employed for diagnosis of RSV infection in adults with variable results (1, 27, 42, 44, 74). In one nursing home study, an IgG EIA using purified F and G glycoproteins was positive for 85% of culture-positive individuals (44). In the seronegative infections, constant high titers were noted and may indicate that illness was present for several days prior to collection of the acute-phase sera, when IgG titers may have already risen, thus obscuring a fourfold titer rise. When pre-illness sera are available, we have found sensitivity to approach 100% using this assay (unpublished data). Nevertheless, false-negative results may occur, particularly when evaluating adults on admission to the hospital, since illness has often been present for a number of days prior to evaluation. Detection of IgM in acute-phase sera may be of value in this situation and would also provide an immediate diagnosis of RSV, but at present these assays are not readily available (27, 35, 177). Vikerfors detected RSV-specific IgM in the serum of 81% of RSV-infected, hospitalized adults with lower respiratory tract illness (177). IgM was present between 6 and 40 days after the onset of symptoms in this study. Similarly, Dowell reported that 58% of adults with serologically confirmed RSV pneumonia had virus-specific IgM in acute-phase sera (27). Additionally, he found that 19% of those with stable high-titer IgG titers to RSV were also IgM positive upon admission to the hospital.

RT-PCR

RT-PCR has recently been described as a useful diagnostic tool in infants, but there are no published reports for adult populations (56, 95, 176). Freymuth, using primers to the conserved regions of the N or NS2 gene, found RT-PCR to be 97.5% sensitive in 80 culture-positive samples from infants (56). In addition he identified RSV RNA in 57 of 158 culture-negative specimens. Similar results have been noted by other investigators (95, 176). In an analysis of 30 serologically proven RSV infections in adults, RT-PCR was positive in 12 of 13 (92%) culture-positive samples, also detected 7 of 17 culture-negative samples from seropositive illnesses, and was negative for all 20 culture-negative, seronegative samples (A. R. Falsey, E. E. Walsh, and M. A. Formica, *Abstr. 39th Intersci. Conf. Antimicrob. Agents Chemother.*, abstr. H-71, 1998). There are no reports on the utility of RT-PCR in diagnosis of RSV infection in immunocompromised adults, although it would be logical that this technique may be more sensitive and rapid than existing methods.

TREATMENT

Elderly Patients

Depending upon the circumstances, both supportive and specific antiviral therapy should be considered in the management of RSV infection in the adult. Supportive therapy includes fluids and oxygen. Although bronchodilators and corticosteroids have not been proven to be of benefit for infants with bronchiolitis, their use in adults with asthma or COPD and evidence of bronchospasm seems reasonable. The use of antibiotics may be prudent in selected RSV-infected persons who have bacterial pathogens isolated from sputum. Currently, aerosolized ribavirin is the only approved agent for treatment

of RSV. Its use in infants is somewhat controversial, since placebo-controlled randomized trials have not always demonstrated efficacy, and current recommendations are that clinicians consider the use of ribavirin therapy in specific high-risk individuals. In addition to ribavirin, two immunoglobulin preparations (polyclonal high-titered RSV immunoglobulin and a humanized F-specific monoclonal antibody) are approved for prophylaxis of RSV infection (24, 70, 71). In contrast to infants, in which both ribavirin and immunoglobulin therapy have been evaluated in placebo-controlled trials, only anecdotal results for relatively small numbers of patients or results of uncontrolled trials exist on their use in adults (26, 33, 34, 49, 53, 89, 97, 122, 168, 174, 188–190). The majority of these reports are on immunocompromised persons, especially BMT recipients, with only anecdotal descriptions of their use in elderly persons.

Antiviral therapy is not warranted at this time for upper respiratory tract symptoms in healthy adults, and symptomatic treatment should be used. However, there may be a need for early specific antiviral therapy in high-risk persons with cardiopulmonary disease or those who are severely immunocompromised, since serious lower respiratory tract involvement develops in a high percentage of these persons (180, 189–191). Unfortunately, rapid diagnostic methods with high sensitivity are lacking, and early definitive therapy is thus frequently not feasible (see above). Anecdotal reports of treatment of the elderly do not provide sufficient evidence to judge efficacy (49, 174). In one report, one of two patients with nosocomial RSV in a surgical intensive care unit died despite 5 days of inhaled ribavirin (49). Nevertheless, it seems reasonable to consider treatment of elderly persons requiring hospitalization for severe disease. Liss and Bernstein evaluated the safety of ribavirin aerosol in eight uninfected elderly volunteers, most with COPD, and found that 8 to 18 h of treatment per day was well tolerated with minimal effect on lung function (117). However, it may be difficult to administer prolonged aerosolized ribavirin therapy by face mask (20 mg/ml for 18 h per day) to elderly persons with cognitive impairment, and high-dose, short-duration therapy (60 mg/ml for 2 h three times per day) should be considered (31).

Immunocompromised Patients

Immunocompromised patients with lower respiratory symptoms should always be considered for specific antiviral therapy, since mortality rates are high, especially among BMT recipients who become infected prior to marrow engraftment. Uncontrolled studies of intravenous, oral, or aerosolized ribavirin treatment with or without immunoglobulin infusions have been reported (26, 33, 34, 49, 53, 89, 97, 115, 122, 125, 166, 168, 174, 188–190). Use of aerosolized ribavirin alone to treat RSV pneumonia in BMT recipients has been associated with 70% mortality, which is not significantly different from historical controls (89, 97). Combination therapy with high-titered RSV immunoglobulin plus aerosolized ribavirin (20 mg/ml for 18 h per day) was used in 16 BMT patients with RSV pneumonia, with a mortality rate of 50% (189). Intravenous ribavirin therapy does not appear to be effective and was associated with an 80% mortality in one study (115). Initiation of therapy at least 1 day prior to the onset of respiratory failure is an important factor for success, since mortality rates are 100% in patients treated after the onset of respiratory failure (188). Treatment of BMT patients with upper respiratory tract infection, especially if they occur prior to engraftment, is reasonable given the high rate of progression to pneumonia. In one study, Bowden treated 25 BMT patients with RSV upper respiratory tract

infection with ribavirin for 2 h per day for 7 days in an attempt to prevent spread to the lower respiratory tract (13). Although the regimen failed to reduce virus shedding, only 32% went on to develop pneumonia, compared to 50 to 60% in historical controls, and among those who developed pneumonia, the mortality was 29%, compared to the 80% noted historically. One approach which uses early intervention with ribavirin with or without RSV immunoglobulin is currently being evaluated by the Collaborative Antiviral Study Group.

PREVENTION

Infection Control

Various infection control strategies, principally handwashing, have been employed to limit the spread of nosocomial RSV (69). Since compliance with handwashing is frequently poor, some authorities advocate the use of gowns and gloves, which have been associated with reduced nosocomial RSV infection rates on pediatric wards (118). Masks are not warranted in the control of RSV since transmission is not via aerosol and ordinary masks cover only one potential route of autoinoculation, the nose. An unusual approach of using eye-nose goggles to prevent infection of staff has been shown to limit RSV spread (58). If possible, isolation and cohorting of infected patients is also recommended (69). Education of staff regarding transmission of respiratory viruses and the value of handwashing was associated with reduced rates of acute respiratory tract infections in a senior daycare center (41). In view of the devastating effects of RSV infection in immunocompromised hosts, very aggressive infection control strategies have been employed and have been shown to be effective in reducing nosocomial RSV infection rates. By utilizing certain measures, the rate of RSV infection was reduced from 4.4 to 1.0 case per 1,000 patient-days at M. D. Andersen Cancer Center. The infection control measures used in BMT units include screening of ill patients with rapid diagnostic tests; early isolation, cohorting, and treatment of infected patients; use of gowns, gloves, and masks when caring for infected patients (to be used during close contact [<1 m] for all BMT patients during community outbreaks); strict handwashing; screening of visitors for respiratory symptoms; prohibition of visits from children <12 years old; prohibition of ill staff members from working on the BMT unit; and staff education.

Vaccination

For the elderly and those with underlying cardiopulmonary disease, immunization may provide the best potential for prevention. Although there is no licensed RSV vaccination at this time, several approaches to immunization are in progress. Most vaccine studies to date have involved children, and a recent review by Dudas and Karron summarizes the current experience with RSV vaccines (28). Data from studies involving adults are much more limited. Immunization with purified subunit F protein (PF2-2; Wyeth-Lederle) induced moderate increases in neutralizing antibodies in healthy elderly subjects (45). Sixty-one percent of subjects developed a fourfold rise in neutralizing antibody to group A or B virus 8 weeks after vaccination with 50 μ g of purified F on alum. Among institutionalized elderly persons who were considerably older and more frail, immunization induced neutralizing antibody responses in 47% (46). In both studies, low preimmunization neutralizing antibody titer was predictive of response. Another approach to immunization is with live attenuated vaccines given by the intranasal route (106). Several live attenuated

mutants have been safety tested in healthy adults prior to testing in young children and infants, although virus replication and immunogenicity have been variable (127, 154, 185). Combined or sequential immunization with PF2-2 and a cold-passaged temperature-sensitive live attenuated virus (248/404 RSV) was well tolerated in both healthy young and healthy older adults, although immunogenicity was poor (65).

CONCLUSIONS

During the past two decades, a growing number of studies have clearly established RSV as a severe pathogen in certain adult populations. The frail elderly, those with underlying cardiopulmonary disease, and the immunocompromised appear to be at greatest risk of developing severe, even life-threatening disease. Nevertheless, this disease is unrecognized by most internists, in part because the possibility of RSV is not considered but also because diagnosis is difficult to make during the acute illness. Certain groups of adults would benefit from the development of effective new antivirals and vaccines for the treatment and prevention of RSV infection. However, before progress can be made in this field, the epidemiology, immunology, and pathogenesis of RSV illness in the adult need to be further defined using improved methods of diagnosis.

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