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CURRENT OPINION

Respiratory Syncytial Virus Infection in Older Adults: An Under-Recognized Problem

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Abstract Human respiratory syncytial virus (RSV) is an enveloped, single-stranded, negative-sense RNA virus and member of the *Paramyxoviridae* family of the genus Pneumovirus that was first reported as a major pathogen in pediatric populations. However, since its discovery, RSV has not infrequently been detected in adults. Reinfection occurs throughout life, with more severe disease occurring in older adults, immunocompromised patients, and those with underlying cardiopulmonary disease. Initially described as the cause of nursing home outbreaks of respiratory disease, there is a now significant body of literature describing the clinical importance of RSV in older adults in a multitude of settings including long-term care, adult daycares, and in community-dwelling adults. Moreover, recent reports from China and other countries emphasize that RSV is a global pathogen that will become increasingly important in developed nations with aging populations. Annual attack rates in the USA range from 2 to 10 % in community-dwelling older adults and 5–10 % in older adults living in congregate settings. Population-based calculations of the proportion of acute respiratory illnesses attributable to RSV estimate that 11,000 elderly persons die annually in the USA of illnesses related to RSV infection. Clinical manifestations of RSV infections are similar to that of other viral respiratory pathogens and include cough, nasal congestion, rhinorrhea, sore throat, and dyspnea. Lower respiratory tract disease is common and may result in respiratory failure (8–13 %) or death (2–5 %). Recent advances in molecular diagnostics have made it possible to rapidly identify RSV infection using nucleic acid amplification tests, although clinicians will need to suspect the diagnosis when viral activity is high. At the present time, treatment is supportive. Effective antiviral agents for the treatment and vaccines for prevention of RSV remain a significant unmet medical need in the older adult population.

Key Points

Recent reports from the USA and other countries emphasize that respiratory syncytial virus (RSV) is a global pathogen that will become increasingly important in developed nations with aging populations.

Clinical manifestations are similar to that of other viral respiratory pathogens and lower respiratory tract disease is common, often resulting in respiratory failure (8–13 %) or death (2–5 %).

Advances in molecular diagnostics have facilitated rapid identification of RSV infection but effective antiviral agents and vaccines remain a significant unmet medical need.

1 Introduction

Human respiratory syncytial virus (RSV) is an enveloped, single-stranded, negative-sense RNA virus and member of the *Paramyxoviridae* family of the genus Pneumovirus. It

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was first isolated in 1956 and derives its name from a characteristic cytopathic effect of syncytia formation in cell culture. RSV is classified into two major groups—A and B—based on antigenic and genetic analysis [1–4]. It was initially reported as a major pathogen in pediatric populations and is known to cause a significant proportion of moderate to severe respiratory illnesses in young children [5–7]. However, since its initial discovery, RSV has not infrequently been detected in adults [8–16]. Reinfection occurs throughout life, although many illnesses in young healthy adults are relatively mild and rarely necessitate medical attention [17, 18]. More severe disease may occur in older adults, immunocompromised patients, and those with underlying cardiopulmonary disease. Compared to influenza, yearly RSV epidemics are generally more prolonged and occur from late autumn to early spring with predictable yearly activity [19–21].

Recent epidemiological data have revealed that the burden of infection in older adults caused by RSV is similar to non-pandemic influenza, with comparable rates of infection and severity of illness [20, 22]. Furthermore, the impact of RSV infection in adults continues to increase as a result of an aging population and the use of immunosuppressive therapies for malignancy and inflammatory disorders. Thus, effective therapeutics agents and vaccines for RSV would be beneficial for older adults as well as children.

2 Epidemiology

Initially described as the cause of nursing home outbreaks of respiratory disease, there is a now significant body of literature describing the clinical importance of RSV in older adults in a multitude of settings, including long-term care, adult daycares, and in community-dwelling adults [11, 15, 23–27]. Many early reports were from North America and Europe but a recent large study from China emphasizes that RSV is a global pathogen that will become increasingly important in developed nations with aging populations [28–32]. Physicians caring for older adults rarely consider the diagnosis of RSV and in the past insensitive methods of detection hampered defining the impact of RSV in adults [33–35]. However, the availability of sensitive molecular testing has provided a much more accurate picture of the true burden of disease [34]. For example, in a study of adults in the UK seen by general practitioners for acute respiratory illnesses, 20 % of patients aged 45–65 years and 15 % of patients older than 65 years were found to have an RSV infection using reverse transcriptase (RT) polymerase chain reaction (PCR) (RT-PCR) [11]. More recent data suggest that adults >65 years old have a higher risk of medically attended RSV infection, which increases with increasing age [27, 36].

Population-based calculations of the proportion of acute respiratory illnesses attributable to RSV have also provided estimates of disease burden in older adults. In one study, Nicholson and colleagues calculated that the wintertime respiratory morbidity due to RSV exceeded that of non-pandemic influenza [9, 10]. Using healthcare databases and viral surveillance methods over a 9-year period, Thompson et al. estimated that 11,000 elderly persons die annually in the USA of illnesses related to RSV infection [8]. Lastly, in a recent US population-based study conducted by the Marshfield Clinic Research Foundation, the overall seasonal incidence of medically attended respiratory illnesses (MARI) due to RSV among community-dwelling adults over four winter seasons from 2006 to 2010 was determined to be 154 episodes per 10,000 persons [37].

2.1 Community-Dwelling Elderly

Data on RSV infection rates among community-dwelling older adults is somewhat limited since most studies have focused on nursing home residents or hospitalized patients. However, several prospective studies have been performed and indicate infection rates are generally 2–10 % each year [14, 20]. In a US study of 608 healthy persons older than 65 years and 540 high-risk patients with cardiopulmonary disease over a 4-year period, RSV infection was identified in 3–7 % of healthy subjects and 4–10 % of high-risk patients using a combination of RT-PCR and serology [14] (Fig. 1). Most infections were symptomatic (90 %) and the need for medical attention was significantly greater in those with high-risk conditions. Half of those subjects sought medical attention and 16 % were hospitalized. Lower rates of infection (2–3 %) were reported in an RSV vaccine study of approximately 1000 older adults with cardiopulmonary diseases, although rates were similar to influenza infection (3–4 %) during the study period [38]. In a recent influenza vaccine efficacy surveillance conducted from 2008 to 2009, 556 persons with moderate to severe illnesses (defined by the presence of at least one respiratory symptom, i.e., cough, congestion, sore throat, or dyspnea, and one systemic symptom, i.e., headache, fatigue, myalgia, feverishness, or fever) were evaluated for RSV infection and 7.4 % were found to be RT-PCR positive [20]. Of note, the incidence of RSV detection increased with age, occurring in 6.1 % of subjects aged 65–69 years with influenza-like illness, 7.1 % aged 70–74 years, and 8.7 % of subjects aged 75 years or older.

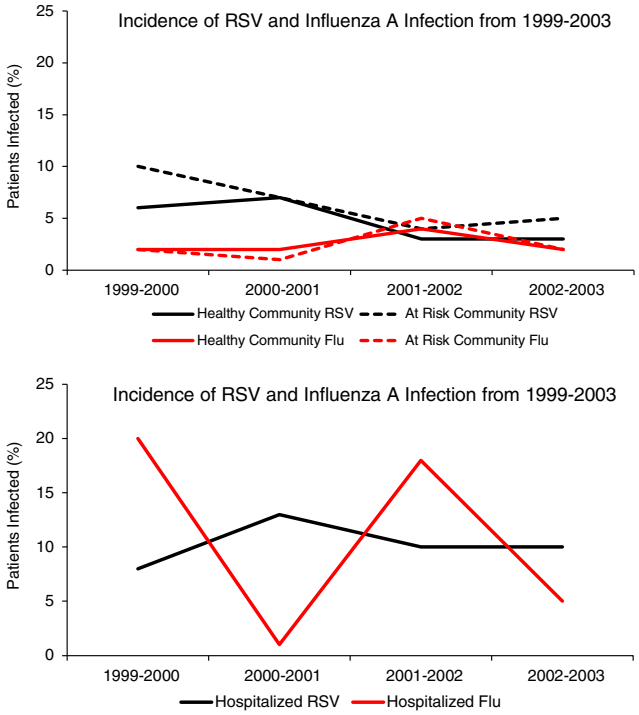

Fig. 1 Incidence of respiratory syncytial virus and influenza infection in a prospective study of three cohorts of older adults over four winters from 1999 to 2003: healthy older adults living in the community ($n = 212$, 280, 180, and 295 for each winter, respectively) (**a**); at-risk older adults living in the community with underlying cardiopulmonary disease ($n = 206$,271,195, and 210) (**a**); and older adults hospitalized with respiratory illnesses ($n = 274$, 296, 434, and 384) (**b**) [14]. *RSV* respiratory syncytial virus

2.2 Long-Term Care Facilities

In contrast to studies of community-dwelling individuals, RSV infections in older adults living in congregate settings such as long-term care facilities and those attending day-care programs have been reported extensively, with many published accounts of wintertime outbreaks in these populations. In outbreak settings, attack rates can be very high (80 %), with significant rates of pneumonia (30 %) and death (5 %) [15, 23–25, 39–48]. Ellis et al. conducted a population-based analysis of the burden of RSV and influenza infection in 81,885 nursing home residents in Tennessee, USA. Rates of hospitalization due to respiratory illness and death for 4 consecutive years related to viral activity in the community were analyzed and RSV accounted for 15 hospitalizations and 17 deaths per 1000 persons, with an incidence of 7 and 9 %, respectively [25]. Notably, morbidity was higher in patients with co-morbid conditions such as underlying cardiopulmonary disease. RSV is also a relatively common cause of illness among frail older adults attending senior daycare programs. In one 15-month study, 10 % of 165 attendees developed respiratory illnesses secondary to RSV infection [26]. Despite the variable rates of infection and morbidity and mortality reported from nursing homes, the estimated overall rate of infection in congregate settings is estimated to be 5–10 %, resulting in rates of hospitalization and pneumonia of 10–20 % and death rates of 2–5 %.

2.3 Hospitalized Patients

RSV is increasingly recognized as a cause of hospitalization during the winter months for older adults. Pneumonia and exacerbations of chronic medical conditions such as asthma, chronic obstructive pulmonary disease (COPD) and congestive heart failure (CHF) are commonly associated diagnoses [12, 14, 20, 21, 27, 28, 30, 49–56]. The first reports of RSV in older hospitalized patients were from Sweden in the late 1960s, with an incidence of 7 % in older patients hospitalized with pneumonia [57]. Recent studies confirm that the percentage of adult patients hospitalized with acute respiratory illnesses due to RSV varies from 3 to 12 % during the winter [14, 20, 30, 49, 58]. In one analysis of adults in Ohio, USA, hospitalized for respiratory illnesses, RSV was found to be the etiology of respiratory illnesses in 4.4 % of subjects, with similar rates of *Streptococcus* pneumonia (6.2 %) and influenza (5.4 %) identified [58]. In a report of 1471 patients hospitalized with respiratory illnesses evaluated over four winters, a fairly constant rate of RSV infection (8–13 %) was noted, and for two of the four winters RSV infection rates eclipsed influenza infection rates, which were more variable (1–20 %) (Fig. 1) [19]. This study also revealed similar mortality rates for the two viruses at 7 and 8 %, respectively. In a more recent publication, we described similar rates of RSV infection (7 %) in 842 subjects enrolled in a surveillance study of adult patients (>21 years old) hospitalized with respiratory illnesses [22].

Finally, medically attended RSV infection occurs at higher rates in older adults than in younger adults. A recent study of Tennessee residents >18 years old evaluated in the emergency department or hospitalized for respiratory symptoms from 2009 to 2010 illustrates this point, revealing higher rates of hospitalization in patients >50 years of age [27]. A Canadian study found that significant morbidity and mortality were associated with hospitalization secondary to RSV infection, with high rates of intensive care unit care (10–21 %) and mechanical ventilation (2–10 %) and a case fatality rate of 6–10 % [21].

2.4 Immunocompromised Hosts

Finally, as medical care for malignant diseases is provided to increasingly older patients, elderly persons receiving cytotoxic therapy for acute leukemia or those who have undergone hematopoietic stem cell transplant (HSCT) or

solid-organ transplant are at significant risk for severe RSV infections and fatal outcomes [59–66]. In younger adults with severely impaired immunity, mortality related to RSV infection can exceed 90 % and it may be reasonably assumed that this risk may be even greater in elderly patients. RSV infection is most serious in HSCT patients during the pre-engraftment period, with mortality rates ranging from 30 to 70 %. Mortality in this group has been linked to the progression from upper respiratory to lower respiratory tract disease defined by RSV detected in lower respiratory tract secretions and lower respiratory tract symptoms such as cough, oxygen requirement, and wheezing [67]. The observed rates of progression described range from 0 to 60 % [68, 69] and have been associated with certain risk factors, including tobacco use and lymphopenia [67, 70, 71].

3 Clinical Manifestations

The clinical symptoms of RSV infection in older adults are very diverse and range from asymptomatic infection to respiratory failure and death. Typically, after an incubation period of 3–5 days, symptomatic respiratory illnesses begins with coryza type symptoms. In general, the clinical manifestations of RSV infection are similar to those of other viral respiratory pathogens and include cough in >90 % of episodes, nasal congestion and rhinorrhea (22–78 %), sore throat (16–64 %), and dyspnea (51–93 %) (Table 1). Although there is significant overlap in symptoms, the presence of rhinorrhea and wheezing is suggestive of RSV, whereas fever of >38 °C more frequently occurs with influenza infections [20, 21, 27, 36].

In all studies, the highest risk of severe disease appears to be for patients with underlying cardiopulmonary disease and is associated with the development of lower respiratory tract symptoms and pneumonia [53–55, 72–78]. In an assessment of risk factors for severe disease, as defined by hospitalization, the presence of COPD, functional impairment, and low serum-neutralizing antibody were independently associated with severe disease [55, 74, 79]. Lower respiratory tract disease is common and respiratory failure may develop in 8–13 % of hospitalized patients [14, 21]. Radiological evidence of pneumonia is noted in 30–50 % of cases [14, 21, 30, 58, 80]. Generally, infiltrates are unimpressive and defined by the presence of unilateral or bilateral patchy sub-segmental alveolar infiltrates, although in one study lobar consolidation was noted [14, 21, 30, 58, 80]. The majority of these infections are presumed to be viral alone, although the precise rate of co-infection with bacterial pathogens has not been clearly defined as a result of imprecise diagnostic testing for bacterial respiratory pathogens. Furthermore, most studies do not systematically collect bacterial cultures. Limited reports, however, estimate that bacterial co-infection occurs in 10–30 % of RSV-associated hospitalizations [14, 21, 30, 58, 80]. In a recent retrospective study of adults admitted to three acute care facilities in Hong Kong with confirmed RSV infection, the rate of bacterial superinfection at the time of presentation was 12.5 % and the organisms identified included *Streptococcus pneumoniae*, (15/76), *Haemophilus influenzae* (14/76), *Staphylococcus aureus* (5/76), *Moraxella catarrhalis* (2/76), *Pseudomonas aeruginosa* (20/76), and *Klebsiella* species (10/76) [30]. In another study conducted in the UK, 3–4 % of invasive pneumococcal disease was associated with recent RSV infection compared with 6–7.5 % associated with influenza co-infection [81]. Similarly, in the study by Falsey et al. [14] evaluating RSV infection in elderly and high-risk adults, rates of bacterial co-infection identified by positive sputum cultures obtained for routine care were similar for patients hospitalized with influenza and RSV (12 vs. 15 %, respectively). Finally, a recent comprehensive evaluation of bacterial complications of viral infections in hospitalized adults using a combination of biomarkers and extensive bacterial testing found that 31 % of RSV infections were associated with bacterial infections [22]. It is therefore recommended that persons infected with RSV be assessed for bacterial complications, though pre-emptive antibacterials are not recommended in uncomplicated cases.

Table 1 Clinical manifestations of respiratory syncytial virus infection compared with symptomatic influenza A disease [20, 21, 27, 36]

Symptoms	RSV (%)	Influenza (%)
Cough	85–95	89
Dyspnea	51–93	32
Wheezing	33–90	30
Rhinorrhea	22–78	64
Sore throat	16–64	64
Myalgias	10–64	70
Fever	48–56	72

RSV respiratory syncytial virus

4 Diagnosis

Diagnosis of RSV in adults is problematic due to the nonspecific nature of the clinical features and, thus, clinicians need to consider the diagnosis when viral activity is high. Definitive diagnosis requires laboratory confirmation, which can be accomplished by a number of methods including viral culture, rapid antigen testing, and RT-PCR [82].

A significant challenge to making a diagnosis of RSV infection is that adults with re-infection shed virus at

considerably lower titers and for a shorter duration of time than in children. Typically, adults shed virus in their nasal secretions for 3–4 days at titers of 10^1–10^3 pfu/mL compared with titers in children that may be as much as 1000-fold higher and for more prolonged periods [83, 84]. Therefore, the low levels of virus shed by adults as well as the thermolability of RSV contribute to the insensitivity of viral culture and rapid antigen detection with enzyme immunoassays (EIAs) in this age group [34, 85]. When performed under ideal conditions with a short lag time from sampling to inoculation, the sensitivity of viral culture is approximately 50 % and of rapid antigen tests is 20 % compared with serology or RT-PCR. In one study of nursing home residents, RSV was isolated from viral cultures in 45 % of serologically confirmed cases of RSV [15]. In a second study evaluating the sensitivity of three rapid antigen tests to detect RSV, a diagnosis was made in 10–23 % of proven cases by RT-PCR, culture, or serology [33].

Serological methods based on EIA using purified virus or viral proteins such as the G and F glycoprotein appear to be more reliable in older adults, which may be due in part to the as yet unexplained observation of a more a vigorous IgG antibody response in adults older than 65 years than in younger adults [86]. Although IgG serology has been shown to be very sensitive (90–95 %), it is only useful in research settings since a $\geq$4-fold rise in titer (acute to convalescent) is needed for diagnosis [14, 34]. At the present time, there are currently no reliable IgM EIA assays in clinical use [82].

In contrast to the insensitivity of culture and antigen assays and the poor clinical utility of serological tests, molecular assays (nuclear acid amplification tests; NAATs) have become the gold standard in respiratory virus detection offering both high sensitivity and specificity (Table 2). Widespread availability of uniplex RSV PCR assays, combined influenza and RSV PCR assays, and more recently a variety of multiplex RT-PCR assays that are able to detect as many as 15 common respiratory viruses now allow for rapid viral diagnosis with a turnaround time as short as 1 h for some assays. Disadvantages of RT-PCRs assays include the relatively high cost, which may prohibit use in smaller community hospitals, and the variation in cut-off thresholds for the different assays, which to date have not been standardized. Although commercial assays are approved for nasopharyngeal samples, recent findings indicate that performing RT-PCR of diluted sputum increases the diagnostic yielded by 29 %, with viral titers nearly double that of the paired nasal secretion sample [87]. Thus, at presentation for medical care, the virus may have progressed to the lower airways in older adults with undetectable titers in the traditionally used nasal secretion samples.

Table 2 Sensitivity of viral culture, antigen testing, and serology compared with reverse transcriptase polymerase chain reaction for respiratory syncytial virus infection [14, 15, 33, 34, 82, 85]

	Sensitivity (%)	Specificity (%)
Viral culture	45–50	100
EIA antigen tests	10–23	75–95
Serology		
IgG	90–95	90–95
IgM	58–80	NA

EIA enzyme immunoassay, *NA* not available

5 Treatment

Treatment for RSV infection is generally supportive, consisting of therapy with bronchodilators, supplemental oxygen, intravenous fluid, and antipyretics. Inhaled and systemic corticosteroids have also been used with variable response and are frequently prescribed in patients with underlying lung disease such as asthma or COPD presenting with acute exacerbation associated with wheezing and bronchospasm. Though there are no reports indicating differences in viral shedding or cell-mediated immunity, humoral immunity may be slightly diminished with the use of systemic corticosteroids, and therefore the potential benefits should be weighed against the severity of the viral illness [88].

Although severe disease in older adults is clearly linked to the presence of chronic conditions and frailty, there is a modest but growing literature demonstrating the importance of the virus [4, 84, 89]. In a study of hospitalized older adults, nasal secretion RSV viral titers, as measured by quantitative RT-PCR, were significantly higher in patients that required mechanical ventilation than in those that did not (3.7 ± 1.7 vs. 2.4 ± 1.1 pfu/mL) [84]. In a subsequent study severe disease, as defined by hospitalization, was characterized by longer viral shedding than in more mildly ill outpatients [89]. Though prolonged viral shedding appears to be associated with severe clinical disease, the underlying mechanism may be related to intrinsic viral properties, inadequate host response to clear infection, or a combination of both.

At the present time, options for antiviral treatment are very limited. The only approved therapeutic option to treat RSV infections in children is the nucleoside analog ribavirin, though its use has been constrained by challenges with administration, cost, and its toxicity profile. In adult populations, the use of ribavirin is off-label and has been limited to severely immunocompromised subjects, in particular HSCT patients. There are no large controlled trials demonstrating efficacy. Data from retrospective reports, a

few prospective studies, and one small randomized controlled trial indicate that therapy with aerosolized ribavirin with and without intravenous immunoglobulin (IVIg) may prevent progression to lower respiratory tract infection (LRTI) as well as decrease mortality in patients with LRTI [70, 90, 91]. Oral ribavirin has also recently been considered as a potential therapeutic agent in HSCT patients and anecdotal and retrospective reports suggest that it may offer some mortality benefit in combination with the use of IVIg [92]. Finally, the immunomodulator palivizumab is an RSV-specific monoclonal antibody directed against the F glycoprotein of RSV that has been shown to reduce viral titers in pulmonary tissues and viral replication in animal models [93, 94]. Palivizumab was approved by the FDA in 1998 for use as prophylaxis in very young high-risk children (aged <2 years) when the randomized IMpact-RSV clinical trial demonstrated significant reduction in hospitalization rates when compared with placebo [95]. There are no data, however, regarding the efficacy of palivizumab as treatment once infection has been established in children or adults [96, 97]. Treatment in adults would also be prohibitively expensive, with costs of US$ 8000 per dose or more reported [97]. It is sometimes used in combination with aerosolized ribavirin in HSCT patients and some studies have demonstrated decreased mortality and progression to lower respiratory tract disease [91].

Among the many therapeutic agents in development, preliminary data on the efficacy of an oral antiviral fusion inhibitor GS-5806 in modulating RSV infection show promise. In an adult challenge model, administration of the drug significantly decreased viral replication as well as reduced symptoms [98, 99]. This agent is currently being tested in a phase IIb randomized, double-blinded, placebo-controlled clinical trial of adult HSCT recipients with an acute RSV LRTI. The purpose of the trial is to determine the effect of GS-5806 on RSV viral load, rates of respiratory failure and all-cause mortality, and the pharmacokinetics, safety, and tolerability of GS-5806 (ClinicalTrials.gov NCT02254421 [106]).

One barrier to the development of newer therapeutic agents has been that efforts to halt viral replication once infection has been established does not moderate the host inflammatory response. Boukhvalova et al. [100] showed that the combination of an antiviral plus an anti-inflammatory agent was most beneficial compared with either agent alone in an aged mouse model. In addition, some strategies target the F glycoprotein, which undergoes structural rearrangement to facilitate fusion of the viral coat with cell membrane and entry of the virus into the cell. An intranasal RSV F-specific immunoglobulin is currently being evaluated for prophylaxis and treatment of RSV, which in animal models blocked both viral replication and pulmonary inflammation [101, 102].

6 Prevention

Currently, there is no licensed vaccine to prevent RSV infection in children or adults. One of the major challenges for adult vaccine development is the difficulty of designing proof-of-concept trials since attack rates are relatively low. Several approaches for adult vaccination have been considered and several candidates are currently in phase I and II clinical trials as well a number of others in the preclinical stage [102]. Live attenuated virus vaccines have not been shown to be immunogenic in older adults, likely in part due to partial immunity [102, 103]. In contrast, subunit vaccines using the purified F protein have been shown to be immunogenic in older adults, including those with COPD and CHF, and are currently in phase II clinical trials [38, 104, 105].

7 Conclusion

RSV has now conclusively been shown to be an important pathogen in older adults and is being recognized as a threat worldwide. Although yearly attack rates are relatively low, the disease burden is large and growing with the aging population. The morbidity and mortality due to RSV infection for this at-risk population rivals that of non-pandemic influenza. Recent advances in molecular diagnostics have made it possible to rapidly identify RSV infection. Effective antiviral agents for the treatment and vaccines for prevention of RSV constitute a significant unmet medical need in the older adult population.

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