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Miscellaneous Topics

The current state of infection with respiratory syncytial virus in the setting of congenital cardiac malformations

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ALONG WITH PREMATURITY AND CHRONIC LUNG disease, the presence of congenital cardiac disease in infants and young children is a significant risk for the clinical consequences of an illness produced by infection with the respiratory syncytial virus.[1] In this review, we present a current understanding of such illnesses, their prevention, and their treatment.

Background

The respiratory syncytial virus is a member of the family *Paramyxoviridae*, which includes such notable human viruses as measles, mumps, parainfluenza, and the newly described metapneumovirus (for review, see Ref. [2]). The virus is pleomorphic in shape and size, with an average diameter of 120 to 300 nanometers. It consists of a nucleocapsid containing a non-segmented, single-stranded ribonucleic acid genome and a surrounding lipid-rich envelope (see Fig. 1). Two surface glycoproteins, the F and G proteins, are most important in the pathogenesis of and the immune response to the virus. The G protein is responsible for the attachment of the virus to the host cell, while the F protein allows for penetration of the virus into the cell by fusing viral and cellular membranes. Unlike influenza and parainfluenza viruses, these glycoprotein spikes possess no hemagglutinating or neuraminidase activities. Viral replication occurs solely in the cytoplasm of the infected host cell, with the F protein promoting spread of the virus from cell to cell through syncytial formation. There are two antigenic subgroups of the virus, the A and B forms, that circulate simultaneously during outbreaks

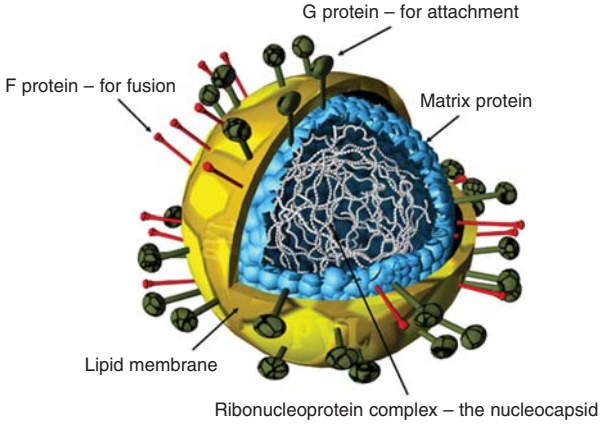

Figure 1.
Schematic representation of the respiratory syncytial virus. The G protein is responsible for the attachment of the virus to the host cell while the F protein allows for penetration of the virus into the cell by fusing viral and cellular membranes. The cartoon is reproduced by kind permission of Professor Andrew J. Easton, Department of Biological Sciences, University of Warwick, Coventry, United Kingdom. www.template.bio.warwick.ac.uk/staff/easton/. Copyright in the figure remains vested in the names of Professor Easton and his department.

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within the community, and there is considerable variation in terms of strains within each group. The clinical and epidemiological significance of the variants is unclear.

The virus has a worldwide distribution, and infects humans of all ages. It is the single most important cause of serious disease of the lower respiratory tract in infants and young children, and can cause both mild and serious respiratory disease in older children and adults. It accounts for up to nine-tenths of the bronchiolitis, and two-fifths of the pneumonia, in hospitalized infants. The virus is highly contagious, and causes sizable annual outbreaks in the community that begin any time from late fall to early winter in temperate climates, and which last for 4 to 5 months (see Fig. 2 and Table 1). The intensity and timing of the annual outbreaks are quite predictable in a given geographic area. In the United States of America, the peak activity occurs in January and February. Outbreaks can involve nearly half of all families with children, and the circulation of the virus is so efficient

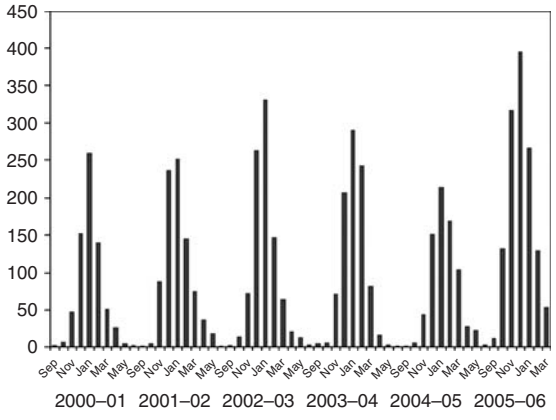

Figure 2.
Monthly reporting of respiratory syncytial virus at The Children's Hospital of Philadelphia. In the northeastern United States of America, peak activity is consistently seen in January and February. The winter season of 2005 through 2006 was particularly active, beginning earlier and infecting more children than in prior years.

that two-thirds of all infants are infected in the first year of life, and virtually all children have been infected by 2 to 3 years of age. The highest rates of attack are seen in infants between 6 weeks and 6 months of age. Reinfections are common, as immunity is imperfect and not completely cross protective against the different antigenic strains. In otherwise healthy older children and adults, reinfections normally result in mild to moderate cold-like symptoms. Very young infants, premature infants, the elderly, and children and adults with chronic illnesses or compromised immune systems are at highest risk for severe and fatal disease. The virus is transmitted by direct close contact with infected persons, aerosolization of large droplets during coughing and sneezing, or indirectly by transfer from surfaces or objects that have been contaminated with respiratory secretions. The eyes and nose are the major portals of entry. The virus can survive on nonporous surfaces, such as cribs and countertops, for up to 12 hours, and for a half-hour or more on hands. Nosocomial infections are of major concern. Controlling the spread of the virus within an institution can be difficult, and careful attention to proper handwashing and infection control guidelines is necessary.

Diagnosis of a disease due to infection with the virus can be made based on epidemiological patterns of activity in the community, together with the clinical symptoms and age of the involved population. This can be difficult, and laboratory confirmation is normally required in patients with serious illness, since signs and symptoms are often overlapping and not specific for any one respiratory virus. This is particularly true in young children. The laboratory diagnosis can be made through isolation of the virus in cell culture, and detection of viral antigens or nucleic acid directly from clinical specimens. Viral cultures, while quite specific, are complex and can be difficult. They are slow, insensitive, time consuming, labor-intensive, and costly. Isolation of virus in culture also requires special conditions for transport and storage of the specimen, since the virus is quite labile outside the

Table 1. Seasonal activity report for infection with respiratory syncytial virus at Children's Hospital of Philadelphia.

	Number of positive detections by month										
Season	Sept	Oct	Nov	Dec	Jan	Feb	Mar	Apr	May	June	Total
2000–01	2	7	47	152	259	140	51	26	5	2	691
2001–02	1	5	88	236	251	145	75	37	18	1	857
2002–03	2	14	72	263	331	147	64	21	13	3	930
2003–04	5	6	71	207	290	242	82	16	3	1	924
2004–05	1	6	44	151	214	169	104	28	23	3	744
2005–06	12	132	317	395	266	129	54	29	13	0	1367

For the 2005–06 season, we used polymerase chain reaction for the first time in combination with rapid antigen and viral culture for the detection of respiratory syncytial virus

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host, and dies quickly if specimens are not kept cold immediately after collection and promptly transported to the laboratory for processing. Immunofluorescent antibody tests, and solid-phase immunoassays, have been successfully employed, and are commercially available for the direct detection of antigens from respiratory secretions. These tests are rapid, with results available in minutes to hours depending on the choice of assays, and economical. They are also sensitive and specific, although generally not as sensitive as cell culture. Increasingly, the polymerase chain reaction is being used as a rapid, sensitive and specific molecular amplification method for the simultaneous detection of nucleic acids from the respiratory syncytial virus and other clinically relevant respiratory viruses.[3] Polymerase chain reaction has been shown to be more sensitive than any single or combined use of rapid antigen tests and culture-based assays for the detection of the virus and other respiratory viruses, and is now considered by many laboratorians to be the new gold standard for testing.

Collection of appropriate material is critical to the success of laboratory testing for respiratory syncytial virus. Specimens should be collected within the first 3 to 5 days of illness, since this is the time of maximum viral shedding. Nasopharyngeal aspirates, or nasal washes, are the preferred specimens of choice because they yield high viral titers and significant numbers of infected columnar epithelial cells. Posterior nasopharyngeal or oropharyngeal swabs, or a combination of the two, may be more practical in adults and older children, particularly if the patient is not cooperative or if large amounts of mucous are not available for aspiration. Tracheal aspirates and bronchoalveolar lavage specimens can also be used in patients with disease of the lower respiratory tract. The laboratory diagnosis must be rapid to impact on patient care and management. The clinical significance of laboratory diagnosis includes:

- aiding in surveillance and control of illness,
- the elimination of inappropriate antimicrobial therapy and unnecessary diagnostic tests and procedures,
- administration of antiviral therapy,
- guiding the management of severely ill patients, and
- educating healthcare workers and informing patients.

Pathophysiology in the patient with congenital cardiac disease

Understanding the consequences of illness produced by the virus in the infant with congenital cardiac disease begins with a review of the anatomy and physiology of the newborn lung. The small airways of the newborn carry a greater intrinsic resistance compared to the mature lung. Even minor compromise creates a significant increase in ventilation workload.[4] Overcirculated lungs, such as those associated with a significant left-to-right shunt, can result in luminal compromise from mucosal oedema of the airway or bronchial compression. In the oligaemic lung, the airways may also be smaller than normal, affecting intrinsic resistance. At the time of birth, furthermore, only a fraction of the full adult complement of alveoluses exists.[5]

For effective gas exchange, the alveolar-capillary interface must remain dry. A variety of safety factors against pulmonary oedema assure a favourable fluid balance in the lung. The factors include, but are not limited to, vascular recruitability, integrity of the interstitial matrix, low endothelial and epithelial oncotic and hydrostatic conductance, active sodium uptake from the alveolus, and effective lymphatic drainage. In the newborn, these safety factors may not be fully functional. To begin with, in contrast to the adult lung, the ability to recruit vascular bed of the newborn lung is very limited. The newborn lung vascular bed is near fully recruited at baseline.[6] Any further increase in flow of blood, coupled with the relatively fixed resistance of a fully recruited vascular bed, results in increased hydrostatic pressure, the primary force behind lung fluid filtration. A cardiac lesion that results in an increase in flow of blood to the lungs must lead to an increase in lung fluid filtration, and a risk of pulmonary oedema.

The integrity of the interstitial matrix and microvasculature of the newborn plays an important role in preventing formation of pulmonary oedema.[7] Hydrophilic proteoglycans in the interstitial matrix, and the high sieving properties of the microvasculature, help to limit fluid and protein filtration into the pulmonary interstitium, and help keep dry the alveolar space. But the capillary endothelium of the newborn lung is prone to microfractures at lower hydrostatic pressure compared to the adult.[8] Consequently, an interruption of microvascular integrity as could occur with severe heart failure or conditions of high pulmonary venous pressure, such as obstructed pulmonary veins, may lead to significant interstitial and airway flooding.

Another safety factor is the epithelial sodium pump, which absorbs sodium ions from the bronchial and alveolar airspace.[9] The osmotic gradient that is created then draws water from the airway to the interstitium. In heart failure, evoked pulmonary inflammatory response, or in the presence of alveolar hypoxia, the activity of these pumps may be impaired.[9]

The oft forgotten vascular bed of the lung is the lymphatic circulation that is responsible for drainage

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of interstitial fluid to the central venous system via the thoracic duct. Increased central venous pressure can impair drainage via the thoracic duct.[10] In the fetal and newborn lamb, flow of lymph from the lungs ceases at much lower central venous pressure than it in the mature sheep.[11] This relative sensitivity to central venous hypertension may explain the altered pulmonary mechanics seen in conditions such as chronic lung disease, for example, bronchopulmonary dysplasia, those with an unstable early bidirectional Glenn anastomosis, and those with right heart failure from congenital cardiac disease or pulmonary hypertension.

Now superimpose upon these immature lungs that are already compromised by heart failure an acute illness produced by the respiratory syncytial virus. Respiratory syncytial viral bronchiolitis leads to bronchial epithelial cell sloughing, impaired production of surfactant, and obstruction to the airways, resulting in the classic radiographic findings of segmental atelectasis and hyperinflation. But the disease process goes well beyond this direct effect. Carpenter and Stenmark[12] have demonstrated that pulmonary oedema occurs in animals with respiratory syncytial viral bronchiolitis, especially in the presence of hypoxia mediated by a perivascular inflammatory response. It appears that the younger the host, the more likely a T helper cell 2 proinflammatory pattern will be incited by bronchial epithelial cellular infection compared to a more mature antiviral T helper cell 1 pattern. The significance of this is that a T helper cell 2 response is characterized by the release of cytokines such as interleukin-4 and interleukin-5, which promote eosinophilia that can further enhance inflammation. Such an inflammatory response may lead to increased oncotic conductance of the microvascular bed with increased transcapillary filtration, thus overloading an already impaired ability to drain the interstitium in the patient with congenital cardiac disease. Furthermore, this inflammatory response can lead to endothelin-mediated alteration of vascular tone, potentially increasing hydraulic conductance.[12] Elimination of water from the lungs may also be affected by the viral illness through impairment of the bronchial sodium pumps.

Finally, there may also be long-term consequences to the airway of infants infected with the respiratory syncytial virus. A link to childhood asthma has been suggested, and a variety of mechanisms, such as local immune memory or neurogenic-mediated pulmonary inflammation, have been proposed.[13,14]

History of prophylaxis

The respiratory syncytial virus was first described by Channock in 1956. Shortly after its description, it became apparent that the virus was a prominent cause of serious bronchiolitis and pneumonia in infants with chronic lung disease, premature infants with a history of oxygen usage, and infants with serious congenital cardiac disease. The specific risk in the setting of congenital cardiac disease was highlighted by MacDonald et al.,[15] who reported deaths of one-third of young children with serious congenital heart disease who had infections during the winter.

There was awareness among virologists that active immunization against the virus might be unsuccessful. In the late 1960s, a vaccine had been developed at the University of Colorado.[16] A preliminary trial with this vaccine showed an increased severity of illness in immunized children who were infected during the subsequent winter. It was, therefore, decided in the late 1980s to investigate passive immunprophylaxis against the virus rather than active immunization.

The first trial of passive immunoprophylaxis was headed by Groothuis,[17] and occurred from 1988 through 1990. For this trial, 249 children were recruited from five centres around the United States of America, with prematurity, chronic lung disease, or serious congenital cardiac disease, about one-third having congenital cardiac disease. The children were given five monthly intravenous infusions each winter of an immunoglobulin preparation chosen from donors with a high titer against respiratory syncytial virus. The enrolled children received either: a control infusion, 150 milligrams per kilogram, or 750 milligrams/kilogram high titer immunoglobulin. The monthly intravenous infusions were effective in preventing hospitalizations due to the virus, but only at the higher dose. Interestingly, there were six deaths during this study, with five of the six were in the one-third of infants enrolled in the study who had congenital heart disease.

The intravenous immunoglobulin used in the study was released in the United States of America in 1994. Because of questions about the deaths in this first study, a separate study of this product limited to children less than two years of age with serious congenital heart disease was undertaken by Simoes et al.[18] from 1993 through 1996. This study, which compared the use of monthly infusions of high titer intravenous immunoglobulin throughout the winter season against uninfused controls, showed efficacy for the high titer intravenous immunoglobulin in infants with significant left to right shunts less than six months of age at the time of enrollment into the study, but failed to show overall efficacy. In addition, there was an increased incidence of unanticipated hypercyanotic episodes and spells, leading to earlier than planned surgery for the cyanotic infants who received the immunoglobulin in this trial. This

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complication of the use of intravenous immunoglobulin in children with cyanotic congenital heart disease limited the use of this first effective product to prevent infection with the virus to infants with acyanotic malformations. In addition, intravenous immunoglobulin was difficult to administer, as it required an infusion of 15 millilitres per kilogram each month, which lasted for three to four hours.

In order to facilitate the passive prophylaxis of the virus, several attempts were made in the 1990s to develop a low dose, intramuscular, monoclonal antibody. The first success in this arena was reported in 1998 in a study limited to premature infants and infants with chronic lung disease.[19] This trial showed for the first time the efficacy and safety of a monoclonal antibody directed against the F protein on the coat of the virus in preventing hospitalizations caused by infection by the virus. This monoclonal antibody (Synagis, MedImmune Inc., Gaithersburg, Maryland) was released in the United States of America in 1998, with the provision that a further study in children with serious congenital heart disease be undertaken. That study was conducted from 1998 to 2002 by Feltes et al.[20] This was the Cardiac Synagis Study, which enrolled 1287 children less than two years of age with serious congenital heart disease in a randomized, double-blind, placebo controlled trial. It showed that this monoclonal antibody was safe and effective in preventing hospitalizations due to respiratory syncytial virus in such children. In addition, there was no increase in hypercyanotic episodes in the cyanotic patients enrolled in this study, making it possible for the monoclonal to be used in all young children with serious congenital cardiac disease.

Current recommendations

Current treatment: Although the respiratory syncytial virus is the major cause of infections of the lower respiratory tract in infants and young children, hospitalization is required for less than 2 percent of this population.[21] Children with hemodynamically significant lesions are at higher risk for this population, and are more likely to require hospitalization and admission to intensive care units.[21–23] Hospitalization for such infants is very high, with one-third requiring admission to the intensive care unit. Mortality remains significant, at 2.5 to 3 percent.[20] Treatment for infection by the virus, especially in those at high risk, remains unsatisfactory. Supportive care remains the mainstay of therapy. Prevention of infections acquired both in the community and nosocomially is becoming increasingly important in an attempt to limit morbidity in this vulnerable population.

Supportive therapies

Oxygen: Prior to the routine use of immunoprophylaxis, rates of hospitalization due to infection with the virus increased significantly, in part due to the routine use of pulse oximetry and the increased finding of hypoxemia (Fig. 3).[24] This has resulted in the routine use of supplemental oxygen to maintain adequate arterial saturation. In acyanotic infants, supplemental oxygen should be given to maintain saturations above 92 percent.[24] In cyanotic infants, for example, those with unrepaired tetralogy of Fallot, and especially those with functionally univentricular hearts with complete intercirculatory mixing, for example following the first stage of Norwood palliation for hypoplastic left heart or functionally univentricular hearts with pulmonary stenosis, supplemental oxygen must be used with care to avoid inadequate systemic or excessive pulmonary blood flows. Similar caution should be exercised in unrepaired infants with large left to right shunts, for example, those with atrioventricular septal defects. Some degree of supplemental oxygen will usually be required to maintain adequate arterial saturation in these neonates if the bronchiolitis is severe, and should be titrated to respiratory effort and to maintain an oxygen saturation between 80 and 85 percent in most children with complete intercirculatory mixing, and above 90 percent in those with large left to right shunts.[24] Supplemental oxygen will not adversely affect the physiology of infants with functionally univentricular hearts who have been palliated with either the superior cavopulmonary or total cavopulmonary anastomosis, and may be used as clinically indicated for work of breathing

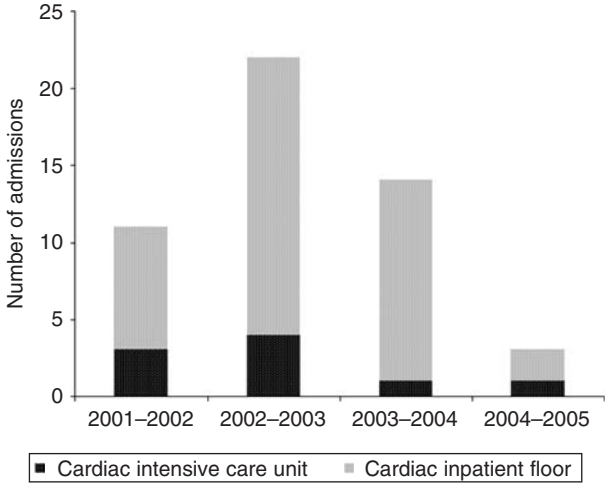

Figure 3.
Since the introduction of routine community immunoprophylaxis, there has been a steady decline in admissions to the cardiac intensive care unit (dark bars) and cardiac stepdown floor (light bars) at The Children's Hospital of Philadelphia. Data reproduced by kind permission of Sarah Tabbutt and Eva Teszner, and we thank them for this courtesy.

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and titrated to appropriate systemic oxygen saturations.

Nasopharyngeal suctioning: Young infants primarily breathe through their nose. Upper airway resistance normally accounts for three-fifths of the resistance of breathing, and will be higher with significant nasal secretions. Nasopharyngeal suctioning to remove secretions has been shown in several studies to be more effective in improving symptoms than bronchodilator therapy.[24,25]

Bronchodilators: Selective β2 agonists, such as nebulized albuterol, are frequently used to treat respiratory syncytial viral bronchiolitis. Data on the effectiveness of these bronchodilators are conflicting. In four meta-analyses of such use in respiratory syncytial viral infection, two studies showed a positive benefit and two show no benefit.[24] The most likely cause for this discrepancy is the heterogeneous population of infants and young children with respiratory syncytial viral bronchiolitis. A significant proportion of the older patients may have had a component of bronchoconstriction due to reactive airway disease. These children may respond favorably to bronchodilators. Others, especially young and first time infected infants, may have bronchoconstriction on the basis of increased secretion and epithelial sloughing and be less likely to respond to bronchodilators. Use of bronchodilators, therefore, should be individualized based on the response of the patient to a trial therapy.

Racemic epinephrine: The large majority of studies of the use of racemic epinephrine in respiratory syncytial viral bronchiolitis have shown positive responses. These responses have included improved arterial oxygen saturation and decreased work of breathing. Racemic epinephrine is an alpha adrenergic agonist and may work by decreasing mucosal oedema especially in a small airway.[24,26] Both bronchodilators and racemic epinephrine must be used cautiously in patients with congenital cardiac disease and known tachyarrhythmias.

Corticosteroids: Most studies that have evaluated the effectiveness of either inhaled or systemic corticosteroids in the treatment of acute respiratory syncytial viral bronchiolitis have failed to show any significant benefit.[24] A meta-analysis of these data did show a small decrease in hospitalization time with steroid use.[27] The inclusion of patients with possible asthma in addition to bronchiolitis in many of these studies make these results difficult to interpret. At best, the effects of steroids on acute respiratory syncytial viral bronchiolitis appear to be small.[23,24,27]

Anti-viral agents

Several anti-vital agents have been evaluated for treatment of acute bronchiolitis due to viral infection. These include Ribavirin, RSV-IGIV (RespiGam™), and palivizumab. Despite great initial enthusiasm for some of these agents, they have had little effect on the course of the disease.[24,28] Much of the reason for this lack of response may be due to the course of viral replication during the bronchiolitis. The viral load peaks at approximately 3 to 5 days after the onset of symptoms. It then falls off despite persistence, and often worsening, of symptoms secondary to the continued inflammatory response.[28] Most infants with bronchiolitis have already passed the point of peak viral load by the time they are hospitalized and antiviral therapy is contemplated.

Ribavirin: Ribavirin is the only anti-viral agent currently approved for treatment of respiratory syncytial viral bronchiolitis. It is a nucleoside analogue, with a wide in vitro response to multiple viruses.[28] Initial studies from the 1980s and 1990s appeared to be quite encouraging.[29,30] Problems with the use of aerosolized water as the placebo in these early studies, as well as the power of the studies to evaluate clinically relevant endpoints, call the results of these studies into question. Recent studies suggest that Ribavirin may have a favorable impact on patients at high risk if it is given early in the course of the disease. A large Canadian study that probably reflects clinical practice failed to show a positive affect of Ribavirin.[31,32]

RSV-IGIV: RSV-IGIV (RespiGam™) is a polyclonal gamma globulin. It has been used as both an acute treatment and as a prophylactic agent. The increase mortality associated with its use in infants with cyanotic heart disease has lead to the recommendation that it not be used in infants with congenital cardiac malformations.[20] In studies with critically ill patients without cardiac disease, time on the ventilator and time in the intensive care unit were reduced by the use of RespiGam™, but there differences were not statistically significant.[28]

Palivizumab: Palivizumab (Synagis™) is a monoclonal antibody that is currently recommended as a prophylactic agent against infection with the respiratory syncytial virus in infants with significant congenital heart disease (see below). Studies of its use to treat acute respiratory syncytial viral bronchiolitis are limited.[28] Although viral load was shown to be decreased in tracheal aspirates of intubated infants by the use of palivizumab, no statistically significant changes were seen in patient outcomes. These findings may be due in part to the power of the studies to measure significant changes in morbidity.[28,33,34]

Prevention of infection

Given the lack of effective treatment for acute respiratory syncytial viral bronchiolitis, and the high morbidity and mortality of the disease in infants

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with congenital cardiac disease, effective preventive strategies to limit infection have taken on great importance.

Nosocomial Infections: The risk of hospital acquired respiratory syncytial viral bronchiolitis in infants with congenital disease is high. In 1982, McDonald et al.[15] reported that one-fifth of infected patients with cardiac disease acquired their infection nosocomially. Patients who are already hospitalized for other reasons, such as surgery or heart failure, are at particularly high risk for severe cases for respiratory syncytial virus infection.

In the hospital setting, the virus is spread by direct passage of secretions, or in large droplet aerosols from sneezing. Contaminated surfaces are potentially problematic as respiratory syncytial virus may remain active on these surfaces for up to 12 hours. The key to controlling spread of the virus in the hospital setting is strict adherence by the staff and patients to routine infection control procedures. These include, but are not limited to, strict hand washing; appropriate use of gowns, gloves, and masks; appropriate patient isolation and cohorting; appropriate and timely diagnostic screening for infection. Beginning passive immunoprophylaxis in the hospital setting is controversial.[35] Patients who are currently receiving prophylaxis and are admitted should continue to receive prophylaxis as routinely scheduled. Importantly, patients admitted during the peak viral season who are receiving prophylaxis and undergo surgery with cardiopulmonary bypass should receive an additional dose after surgery, as cardiopulmonary bypass reduces serum levels of antibody (see below).

Infections acquired in the community, and current recommendations for children with congenital cardiac malformations

The respiratory syncytial virus is ubiquitous in the setting of the community, and rates of infection approach 100 percent by 2 years of life. As such, it is essentially impossible to protect infants with cardiovascular disease at high risk from exposure to infection with the virus. For this reason, passive immuno-prophylaxis is now recommended for this population.[35] Children under 2 years of age, with haemodynamically significant cardiac malformations, should receive prophylaxis with palivizumab. This population includes those patients requiring medication to control congestive failure, patients with cyanosis, and patients with moderate or greater pulmonary hypertension.[17]

The current guidelines prepared by the American Academy of Pediatrics suggest 5 injections of 15 milligrams per kilogram of palivizumab intramuscularly. The timing of the start of therapy should be based on the epidemiology of the respiratory syncytial virus in the community where the patient resides. Although not currently recommended by the American Academy of Pediatrics, we feel strongly that administration of additional doses during a season may be warranted in certain geographic areas, and in certain patients at high risk who are older than 2 years of age. This is due to the recent trend for the virus to persist in communities beyond its previous seasonal patterns. Cardiologists should be aware of the epidemiology of the virus in their own area, and work with their experts in infectious disease, general pediatricians, family physicians, insurers and other providers of care to ensure that prophylaxis occurs during times of high occurrence of the virus in the community.

Palivizumab is not currently recommended for prophylaxis beyond 2 years of age by the American Academy of Pediatrics. There may be certain cases, nonetheless, where this course is appropriate. Complex congenital cardiac disease may persist beyond two years of age, for example, in patients with pulmonary arterial hypertension, persistent hypoxemia from right to left shunting, patients with the Fontan circulation and elevated central venous pressures, and/or those with coexisting pulmonary disease. Viral infection in these patients may result in hospitalization, severe respiratory distress, or death. Again, it may be necessary for the cardiologist to work with other providers of general health care and insurers to meet the needs for prophylaxis of this special population.

Finally, many infants and children undergoing prophylaxis will require surgery with cardiopulmonary bypass during the viral season. It is important to emphasize that cardiopulmonary bypass decreases the concentration of palivizumab in the serum by almost three-fifths.[20] All patients receiving palivizumab who undergo cardiopulmonary bypass, therefore, should receive an additional dose following the procedure.[35]

References

1. Boyce TG, Mellen BG, Mitchel EF, Wright PF, Griffen MR. Rates of hospitalization for respiratory syncytial virus among children in Medicaid. J Pediatr 2000; 137: 865–870.
2. Hall CB. Respiratory syncytial virus and parainfluenza virus. N Engl J Med 2001; 344: 1917–1928.
3. Henrickson KJ. Advances in the laboratory diagnosis of viral respiratory disease. Pediatr Infect Dis J 2004; 23: S6–S10.
4. Hansen T, Corbet A. In: Taeusch HW, Ballard RA (eds). Avery's Diseases of the Newborn. WB Saunders, Philadelphia, 1998, pp 541–667.
5. Inselman LS, Mellins RB. Growth and development of the lung. J Pediatr 1981; 98: 1–15.
6. Feltes TF, Hansen TN. Effects of an aorticopulmonary shunt on lung fluid balance in the young lamb. Pediatr Res 1989; 26: 94–97.
7. Miserocchi G, Negrini D, Passi A, De Luca G. Development of lung edema: interstitial fluid dynamics and molecular structure. News Physiol Sci 2001; 16: 66–71.

https://doi.org/10.1017/S1047951106001077 Published online by Cambridge University Press

8. Fu Z, Heldt GP, West JB. Increased fragility of pulmonary capillaries in newborn rabbit. Am J Physiol Lung Cell Mol Physiol 2003; 284: L703–L709.
9. Matthay MA, Folkesson HG, Clerici C. Lung epithelial fluid transport and the resolution of pulmonary edema. Physiol Rev 2002; 82: 569–600.
10. Drake R, Giesler M, Laine G, Gabel J, Hansen T. Effect of outflow pressure on lung lymph flow in unanesthetized sheep. J Appl Physiol 1985; 58: 70–76.
11. Johnson SA, Vander Straten MC, Parellada JA, Schnakenberg W, Gest AL. Thoracic duct function in fetal, newborn, and adult sheep. Lymphology 1996; 29: 50–56.
12. Carpenter TC, Stenmark KR. Predisposition of infants with chronic lung disease to respiratory syncytial virus-induced respiratory failure: a vascular hypothesis. Pediatr Infect Dis J 2004; 23(Suppl): S33–S40.
13. Sigurs N, Bjarnason R, Sigurbergsson F, Kjellman B. Respiratory syncytial virus bronchiolitis in infancy is an important risk factor for asthma and allergy at age 7. Am J Respir Crit Care Med 2000; 161: 1501–1507.
14. Piedimonte G. Contribution of neuroimmune mechanisms to airway inflammation and remodeling during and after respiratory syncytial virus infection. Pediatr Infect Dis J 2003; 22 (Suppl): S66–S74; discussion S74–S75.
15. MacDonald NE, Hall CB, Suffin SC, Alexson C, Harris PJ, Manning JA. Respiratory Syncytial virus infection in infants with congenital heart disease. N Engl J Med 1982; 307: 397–400.
16. Fulginiti VA, Eller JJ, Sieber OF, Joyner JW, Minamitani M, Meiklejohn G. Respiratory virus immunization I. A field trial of two inactivated respiratory virus vaccines: an aqueous trivalent parainfluenza virus vaccine and an alum-precipitated respiratory syncytial virus vaccine. Am J Epidimeol 1969; 89: 435–448.
17. Groothuis JR, Simoes EAF, Levin MJ, et al. Prophylactic administration of respiratory syncytial virus immune globulin to high-risk infants and children. N Engl J Med 1993; 329: 1524–1530.
18. Simoes EA, Sondheimer HM, Top Jr FH, et al. Respiratory syncytial virus immune globulin for prophylaxis against respiratory Syncytial virus disease in infants and children with congenital heart disease. J Pediatr 1998; 133: 492–499.
19. Impact-RSV Study Group. Palivizumab, a humanized respiratory syncytial virus monoclonal antibody, reduces hospitalizations from respiratory syncytial virus infections. Pediatrics 1998; 102: 531–537.
20. Feltes TF, Cabalka AK, Meissner HC, et al. Palivizumab prophylaxis reduces hospitalization due to respiratory syncytial virus in young children with hemodynamically significant congenital heart disease. J Pediatr 2003; 143: 532–540.
21. Kneyber MCJ, Moons KGM, deGroot R, Moli HA. Prediction of duration of hospitalization in respiratory syncytial virus infection. Pediatr Pulmon 2002; 33: 453–457.
22. Buckingham SC, Quasney MW, Bush AJ, DeVincenzo JP. Respiratory syncytial virus infections in the pediatric intensive care unit: clinical characteristics and risk factors for adverse outcomes. Pediatr Crit Care Med 2001; 2: 318–323.
23. Panitch HB. Bronchiolitis in infants. Curr Opin Pediatr 2001; 13: 256–260.
24. Black CP. Systematic review of the biology and medical management of respiratory syncytial virus infection. Resp Care 2003; 48: 209–230.
25. McKinley G, Ballard J, Salyer J. The effect of NP suctioning on symptom scores in bronchiolitis patients (abstract). Respir Care 2001; 47: 1071.
26. Barr FE, Patel NR, Newth CJ. The pharmacologic mechanism by which inhaled epinephrine reduces airway obstruction in respiratory syncytial virus-associated bronchiolitis. J Pediatr 2000; 136: 699–700.
27. Garrison MM, Christakis DA, HarveyE, Cummings P, Davis RL. Systemic corticosteroids in infant bronchiolitis: a meta-analysis. Pediatr 2000; 105: E44.
28. Jafri HS. Treatment of respiratory syncytial virus: antiviral therapies. Pediatr Inf Dis J 2003; 22: S89–SS93.
29. Hall CB, McBride JT, Gala CL, Hildreth SW, Schnabel KC. Ribavirin treatment of respiratory syncytial viral infection in infants with underlying cardiopulmonary disease. JAMA 1985; 254: 3047–3051.
30. Meert KL, Sarnik AP,Gelmini MJU, Lieh-lei MW. Aerosolized ribiviran treatment in mechanically ventilated children with respiratory syncytial virus lower respiratory tract disease: a prospective, double blind, randomized trial. Crit.Care Med 1994: 22: 566–572.
31. Law BJ, Wang EE, Mac Donald N, et al. Does ribavirin impact on the hospital course of children with respiratory syncytial virus (RSV) infection: an analysis using the pediatric investigators collaborative network on infections in Canada (PIC-NIC) RSV database. Pediatr1997; 99: e7.
32. Groothuis JR, Woodin KA, Katz R, et al. Early ribavirin treatment of respiratory syncytial viral infection in high-risk children. J Pediatr 1990; 117: 792–798.
33. Malley R, Devincenzo J, Ramilo O, et al. Reduction of respiratory syncytial virus (RSV) in tracheal aspirates in intubated infants by use of humanized monoclonal antibody to RSV F protein. J Infect Dis 1998; 178: 1555–1561.
34. Saez-Llorens X, Moreno MT, Ramilo O, et al. Phase I/II, double-blind, placebo-controlled, multidose escalation trial of a humanized respiratory syncytial virus (RSV) monoclonal antibody (MEDI-493) in children hospitalized with RSV (Abstract 906). Presented at the Society for Pediatric Research, New Orleans, May 1 to 5, 1998: 156A.
35. Committee on Infectious Diseases and Committee on Fetus and Newborn. Revised indications for the use of Palivizumab and respiratory syncytial virus immune globulin intravenous for the prevention of respiratory syncytial virus infections. Pediatr 2003; 112: 1442–1446.

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