Respiratory infections and asthma: current treatment strategies

Miles Weinberger

Infections such as lower respiratory illness potentially contribute to the initiation of asthma and are major factors in recurring acute exacerbations of the condition. Although typical bacterial respiratory pathogens such as *Streptococcus pyogenes*, *Streptococcus pneumoniae* and *Hemophilus influenzae* do not initiate asthmatic exacerbations, data from a subgroup of adults suggest a potential role for *Mycoplasma pneumoniae* and *Chlamydia pneumoniae* in the onset of asthma. Common cold viruses, predominantly respiratory syncytial virus (RSV) in young children and rhinoviruses in older children and adults, are the major causes of acute exacerbations of asthma. These exacerbations are not prevented with maintenance therapies that are used for chronic asthma, but do respond to short courses of systemic corticosteroids. There are continued attempts to produce a successful vaccine and antiviral agents for the treatment of RSV that are more effective and more practical to use than ribavirin, which is currently the only available antiviral for RSV. The prevention and treatment of rhinovirus infections have focused on the major receptor for the virus, intercellular adhesion molecule-1 (ICAM-1), which is located on respiratory epithelial cells. A multivalent, recombinant, antibody fusion protein identified as CFY196 has high avidity for ICAM-1 and has the potential to protect against rhinovirus infection. Another approach for preventing and treating rhinovirus infection uses a recombinant, soluble, truncated form of ICAM-1 in which the transmembrane and intracellular domains of the protein have been deleted. An initial clinical study on this agent demonstrated clinical efficacy in ameliorating the symptoms of experimental rhinovirus infection in volunteers, but did not significantly prevent infection.

Miles Weinberger
Pediatric Allergy & Pulmonary Division
University of Iowa College of Medicine
Iowa, USA
e-mail:
miles-weinberger@uiowa.edu

▼ Infections have long been associated with asthma, and viruses in particular have been implicated in the inception of asthma and have been purported to contribute to the exacerbation of this condition [1]. The most common cause of an initial wheezing episode in infancy is respiratory syncytial virus (RSV). This virus occurs in annual epidemics and infects virtually all children at some point in their first two years of life, with the majority becoming infected during their first year. In a prospective study of 125 normal births in Houston (TX, USA), almost 70% of the infants were infected with RSV during the first year of life, and over 20% of the children developed lower respiratory illness in association with RSV [2]. Although only 10% of the children with lower respiratory illness were hospitalized, these data suggest that there is a substantial risk for infants. A recent report indicated that as many as 3% of infants in the USA are hospitalized annually because of lower respiratory illness as a result of contracting RSV [3].

The symptoms of asthma often manifest after RSV-induced bronchiolitis. Although a quarter to half of the children who were hospitalized with RSV infection were observed in later years to have recurrent wheezing and physician diagnoses of asthma, this occurrence was uncommon among those children who were less severely affected; these children were followed as a control population [4–7]. Thus, when healthy babies become infected with RSV, the majority only exhibits the symptoms of a common cold with nasal discharge. However, a minority of RSV-infected children suffers from bronchiolitis, which is the most common cause of hospitalization during the first year of life. Of those children who develop bronchiolitis, ~25–50% subsequently have symptoms of an intermittent pattern of asthma that is characterized by recurrent wheezing only in association with ensuing viral respiratory infections. Whereas clinical experience and natural history studies suggest that the majority of such children remit later in childhood, some continue to have recurrent or chronic lower airway disease from asthma throughout childhood and some also suffer from these conditions in adulthood (Figure 1) [8].

1359-6446/04/$ – see front matter PII: S1359-6446(04)03239-8

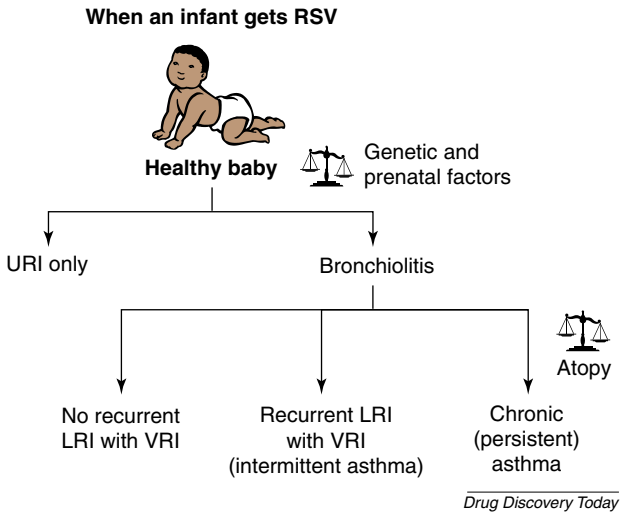

Figure 1. Clinical consequences of initial infection with respiratory syncytial virus in infancy. Data indicate that virtually all children become infected with RSV during the first year of life; the majority of children only contract a URI, the symptoms of which are the same as that of a common cold. Approximately 20% of children infected with RSV, depending on genetic and perhaps also prenatal factors, develop the LRI known as bronchiolitis. For at least half of those, this is an isolated occurrence of the illness, whereas others have recurrent LRI with VRI. Some children that have repeated episodes of LRI, particularly if they have the genetic predisposition to develop allergic antibody in the immunoglobulin E class (commonly identified as atopy), go on to have persistent symptoms that are consistent with a chronic pattern of asthma. Abbreviations: LRI, lower respiratory illness; RSV, respiratory syncytial virus; URI, upper respiratory infection; VRI, viral respiratory infections.

Prevention of morbidity from asthma could therefore benefit from measures that prevent or treat the various infections that precipitate acute exacerbations of asthma. This review addresses the influence of infections on the clinical course of asthma, the current treatment for infection-induced asthma and new therapies that are on the horizon that could potentially benefit asthma therapy by preventing or treating the infection itself.

Influence of subsequent infections on the clinical course of asthma

Viral respiratory infections are a major cause of asthma exacerbations at all ages [9–13], and appear to be the major contributory factor to the large increase in individuals admitted to hospital with symptoms of asthma that is observed every autumn (September–November) in many countries, including the USA, Canada and England [14]. Children of a preschool age have a particularly high frequency of viral respiratory infections, with the majority contracting 3–8 infections per year and 10–15% developing 12 or more per year [15]; this statistic probably explains the substantially higher frequency of asthma hospitalization observed in the preschool age group when compared with older children and adults. Based on data from the US Center for Health Statistics (http://www.cdc.gov/nchs), the annual rate of hospitalization in children who are 1–4 years old has been ~1 in 200 children compared with 1 in 500 children who are 5–14 years old and 1 in 1000 for individuals who are 15–24 years of age [16]. Rates of hospitalization that are similar to these can be found in reports from Singapore [17], Finland [18] and Norway [19].

Epidemiological studies have detected viral upper respiratory infections in 85% of childhood asthma exacerbations [12] and in over half of adult exacerbations [11]; these upper respiratory infections are probably responsible for seasonal peaks of asthma-related hospital admissions [14,20]. Whereas rhinovirus is the most common contributor to exacerbation of asthma in adults and older children, RSV is the most frequent initiator in young children [9,11–13]. Thus, rhinovirus and RSV infections have been linked with asthma inception and exacerbation. The role of the recently described metapneumovirus as a cause of exacerbations of asthma remains to be fully defined, but coughing and wheezing, which are symptoms that are associated with asthma, are frequently reported with this infection [21–24].

Typical respiratory bacterial infections such as *Streptococcus pyogenes*, *Streptococcus pneumoniae* and *Hemophilus influenzae* have not been associated with exacerbations of asthma [9]. However, data have linked *Mycoplasma pneumoniae* and *Chlamydia pneumoniae* with the onset and persistence of asthma [25].

Treatment of respiratory infections associated with asthma

Although antibiotics are often prescribed by practitioners for acute exacerbations of asthma [26,27], this practice is not consistent with the demonstrated absence of typical respiratory bacterial infections that are associated with exacerbations [9]. Moreover, no clinical effect from antibiotics could be demonstrated in randomized double-blind, placebo-controlled trials of acute asthma [28–30]. A potential role for the use of a macrolide antibiotic (clarithromycin) that is effective against *M. pneumoniae* and *C. pneumoniae* has been suggested for a subpopulation of adults with asthma (Figure 2) [31,32]. Although a prolonged course of clarithromycin in patients with positive PCR tests for *M. pneumoniae* resulted in a statistically significant effect on pulmonary function ($P = 0.05$), in patients showing evidence of infection with *M. pneumoniae* or *C. pneumoniae*, the magnitude of effect was small, with the mean forced expiratory volume (FEV_1) in one second, which is a standard

measure of airflow, increasing only modestly from 2.5 to 2.8 l. Because the baseline FEV_1 represented a value that was 69% of the expected value for a normal population of the size, age and sex of the patients, and because the increase would result in a mean that was only ~74% of the expected mean, these results indicate persistence of obstruction to airflow. Moreover, no indication of improved symptom control was reported. Further investigations of the relationship between *M. pneumoniae* and asthma are ongoing. For example, Richard Martin of the Department of Medicine at the National Jewish Medical and Research Center (http://www.njc.org) is the principal investigator on two National Institutes of Health (NIH; http://www.nih.gov) grants relating to the association between *M. pneumoniae* and asthma. Investigators of the Asthma Clinical Research Network (http://www.acrn.org) will have access to one of the grants (funded 2003–2008) to study the link between chronic infection with *M. pneumoniae* and *C. pneumoniae* and chronic asthma (Grant number 1U10HL074073–01). The second grant, which is funded from 2004 to 2009, is a Program Project Grant that comprises 16 investigators separated between four Projects and two Cores to continue research into the link between chronic infection with *M. pneumoniae* and chronic asthma (Grant number 1P01HL073907–01A1). T. Prescott Atkinson (University of Alabama, Birmingham; http://main.uab.edu) has had NIH support to study the incidence of *M. pneumoniae* infections in children with chronic asthma, as well as the host immune response to the infection in those children (Grant 5R01HL061000–04, 2002–2004).

Because of their association with urgent care and hospitalization, the effective treatment of acute exacerbations of asthma from viral respiratory infections is of major importance. Systemic corticosteroids have long been recognized as effective agents for the treatment of acute exacerbations of asthma. However, the tradition for many years was to use them only when it was apparent that vigorous and repetitive use of bronchodilators had failed. Several studies over the past 15 years have demonstrated that the early aggressive use of systemic steroids in children who are having an acute exacerbation of asthma affords a distinct clinical advantage.

Storr *et al.* [33] examined the effect of oral prednisolone in children (mean age of five years) who had been hospitalized with acute asthma. In a randomized double-blind, placebo-controlled trial, 67 children received prednisolone and 73 received placebo shortly after admission. Children who were less than five years old and those who were five years old or older received 30 mg and 60 mg of prednisolone, respectively. Five hours after the beginning of treatment, a decision was made concerning the condition of the children. Of the children who had received prednisolone, 20 could be discharged, compared with only two of those who had received placebo. Among those not discharged at 5 h, a more rapid improvement and earlier discharge occurred in the prednisolone-treated patients than in those who had received placebo.

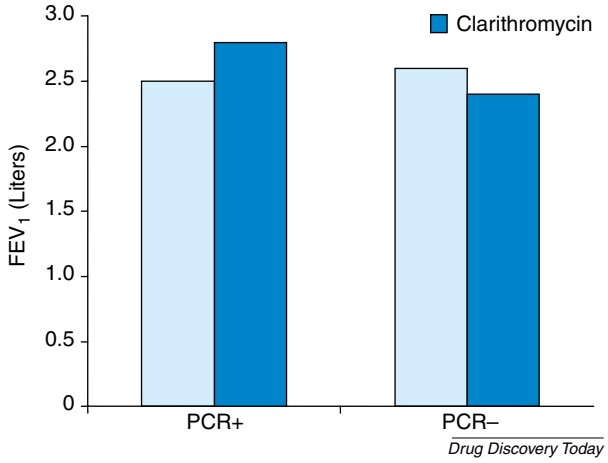

Figure 2. Forced expiratory volume in one second after treatment with clarithromycin. Clarithromycin was administered to 31 asthmatics who were positive (demonstrated by PCR) for *Mycoplasma pneumoniae* or *Chlamydia pneumoniae* and 24 who were negative for the same infections. Dose size of clarithromycin was 500 mg twice daily for six weeks. The difference between the baseline and clarithromycin treatment among the PCR-positive patients was significant ($P = 0.05$), whereas no significant effect was associated with clarithromycin in the PCR-negative patients [32]. Abbreviations: FEV_1, forced expiratory volume in one second.

In another study, Tal *et al.* [34] investigated the efficacy of the administration of systemic corticosteroids to children (0.5–5 years) in a specific age range that was representative of the typical ages of children admitted to emergency rooms suffering from acute asthma [34]. In a double-blind, placebo-controlled trial, the administration of 4 mg kg^{-1} of intramuscular methylprednisolone resulted in a reduction in the number of children admitted to hospital who were examined at 3 h after medication administration; the number of children admitted was reduced from 43% for those dosed with the placebo (normal saline) to 20% of those children to whom methylprednisolone had been administered.

In a similar randomized, double-blind trial in which 36 children (mean age of five years) received 2 mg kg^{-1} of oral prednisone and 39 received placebo, in a mock decision to admit to hospital at 2 h after administration of the treatment, no difference was observed in the number of children admitted to hospital [35]. However, at 4 h, 19 (49%) of the

placebo-treated children were admitted, compared with only 11 (30%) of the prednisone-treated children. The differences were substantially larger for a subgroup that were judged to be the most ill, where 72% of the placebo-treated children were admitted compared with less than half that number among the prednisone-treated children.

Bronchiolitis is often the first viral respiratory infection-induced episode of lower airway obstruction in children who subsequently have asthma exacerbations from the same viruses. However, this condition has been shown to respond to corticosteroids, if a sufficient dose is used [36,37]. Although previous studies at lower doses resulted in equivocal benefit at best, the study by Schuh *et al.* [36] demonstrated a 57% reduction in blinded decisions to hospitalize infants with bronchiolitis that were examined in the emergency department at 4 h after administration of 1 mg kg^{-1} of dexamethasone or placebo.

The value of early administration of oral corticosteroids has been investigated in ambulatory children (median age 12 years) that exhibit occasional acute exacerbations despite being on maintenance medication that controls daily symptoms [38]. Placebo or oral prednisone, administered at dose sizes of 30 or 40 mg twice daily for those below or over age 13, respectively, was started at the onset of an exacerbation, which was defined as symptoms that incompletely respond to bronchodilator. All the 22 prednisone-treated patients subsequently improved, returning to baseline clinical status and normal pulmonary function within seven days. However, eight of the 19 placebo-treated patients exhibited deteriorating status and required further acute intervention.

Brunette *et al.* [32] investigated the value of oral corticosteroids in preventing exacerbations of asthma in a group of children who were less than six years of age and who had a mean of seven hospitalizations in a year for acute viral respiratory infection-induced asthma [39]. Over a period of a year, half of the sample group was treated with prednisone at a dose of 1 mg kg^{-1} day^{-1} at the onset of a viral respiratory infection. The prednisone-treated group, who had averaged 7.6 hospitalizations in the previous year, averaged only 0.7 hospitalizations during the year of treatment. This 90% reduction in the incidence of hospitalization is in contrast to those children not treated with prednisone; these children had a mean of 5.8 hospitalizations in the year before the investigation commenced and averaged 5.9 hospitalizations during the year of the study.

These studies demonstrate that the early administration of systemic corticosteroids for acute asthma permits earlier discharge from the hospital, decreases the probability of admission for those patients seeking urgent care of asthma and prevents progression of exacerbations of asthma in ambulatory patients that are at risk of requiring urgent care. Additionally, the study by Brunette *et al.* [33], although not a blinded placebo-controlled trial like other studies, suggests a high degree of efficacy for the early administration of oral corticosteroids in preventing the early symptoms of a viral respiratory infection from progressing to severe acute asthma in children that are at a substantial risk of requiring hospitalization. Despite previous controversies regarding the use of oral corticosteroids [40], consideration of the data now support the early administration of systemic corticosteroids as the standard of care for acute exacerbations of asthma [41,42]. The safety of repeated courses, which are often required because of the frequency of viral respiratory infections in children, has been demonstrated [43].

Although early intervention for viral respiratory infection-induced exacerbations of asthma is effective, prevention of these episodes would be preferable; this is particularly true for young children who experience a high frequency of viral respiratory infections [15]. Unfortunately, the maintenance medications that are currently available for the treatment of asthma do not preclude these exacerbations of the condition [44]. Even inhaled corticosteroids, which are the most effective maintenance medication for chronic asthma, do not prevent exacerbations and are therefore not indicated for the treatment of asthma that is purely episodic from viral respiratory infections [45–48].

New therapeutic developments

The relative resistance of asthma exacerbations that are triggered by viral respiratory infection to inhaled corticosteroids [49], and evidence that viral respiratory infections are major contributors to asthma [9–13], underline that the role of viral respiratory infections continues to be of major importance. Because RSV is a major cause of respiratory illness in infants and contributes to exacerbations of asthma with repeated infections in early preschool age children, the prevention of this infection has received considerable attention. Administration of passively transferred antibody before exposure decreases, but does not eliminate, the frequency of the occurrence of illness in infants [50,51]. Although initial studies were performed with intravenous γ-globulin (IVIG) that contained high concentrations of RSV antibody, a chimeric mouse–human immunoglobulin G monoclonal antibody, palivizumab [Synagis® (MedImmune; http://www.medimmune.com)], that can be given intramuscularly rather than intravenously has been developed and marketed for use in high-risk infants [52]. However, RSV-antibody that is acquired naturally does not protect against recurrent infection that leads to lower respiratory illness in children

with the asthma predisposition, thus neither the IVIG preparation nor the monoclonal RSV antibody are likely to be of value in preventing recurrent infections that trigger acute exacerbations of asthma.

An effective RSV vaccine would preferably reduce the high frequency of hospitalizations from asthma in young children, as well as providing more complete protection for infants that are at a significant risk of morbidity from the initial infection. Attempts to develop a vaccine have been hindered following early experiences with an alum-precipitated formalin-inactivated RSV vaccine, which led to augmented disease in vaccinees during subsequent natural infection [53,54]; this serious adverse effect was subsequently confirmed by demonstration of enhanced pulmonary histopathology in mice [55,56]. The mechanism of this enhanced pathology has been linked to the induction of type 2 thymic lymphocytes (Th2) that produce those interleukins (IL) that are associated with airway inflammation and eosinophilia (i.e. IL-4 and IL-5) [57]. To overcome the obstacle of adverse effects from previous efforts at vaccine development, live-attenuated and subunit RSV vaccine development is in progress, and recombinant technology is providing additional vaccine candidates [58].

Although an antiviral agent has been marketed for RSV (ribavirin), its modest effect and need for prolonged aerosol administration have resulted in its use being primarily limited to immunocompromised patients. Furthermore, although the early treatment of severe RSV in hospital appears to have some potential for long-term benefit [59], no acute benefit has been observed in the most severe cases [60]. Development of effective and safe orally administered antivirals would therefore be of considerable benefit in the treatment and prevention of initial RSV infections in infants at risk, and perhaps also for young children that are predisposed to suffer repetitive episodes of asthma that are induced by RSV. Multiple agents with low cytotoxicity and highly selective viral-inhibitory activity in cell culture are in discovery and preclinical stages of development, with one agent at Phase II [RFI641 (Wyeth; http://www.wyeth.com)] and two at Phase I [VP14637 (ViroPharma; http://www.viropharma.com) and A60444 (Arrow Therapeutics; http://www.arrowt.co.uk)] [61]. Rhinovirus is the key virus that causes acute exacerbations of asthma beyond early childhood and thus the effective treatment or prevention of that infection would be a major asset in asthma therapy. Interestingly, erythromycin has been shown to inhibit rhinovirus infection in cultured human tracheal epithelial cells, which suggests a potential role for macrolide antibiotics in suppression of this common infectious cause of acute asthma [62]. However, there is no clinical evidence that macrolide antibiotics are effective against rhinovirus infection.

A promising approach to preventing rhinovirus infection has focused on the intercellular adhesion molecule-1 (ICAM-1), which is the single cellular receptor for the majority of rhinovirus serotypes [63,64]. Thus, blockade of that receptor would be expected to prevent rhinovirus infection. Although the early success of a monoclonal blocking antibody to ICAM-1 was limited [65], recent reports of a multivalent recombinant antibody fusion protein from Perlan Therapeutics (http://www.perlan.com), which is known as CFY196, indicates greater avidity for ICAM-1 than previously investigated monoclonal antibodies and consequently confers greater protection against rhinovirus infection in cell culture [66,67]. These reports concluded that further preclinical and clinical development of CFY196 is warranted. Another approach for preventing and treating rhinovirus infection uses a recombinant, soluble, truncated form of ICAM-1 [Tremacamra (Boehringer Ingelheim; http://www.boehringer-ingelheim.com)] in which the transmembrane and intracellular domains of the protein have been deleted. In a randomized, double-blind, placebo-controlled trial, 88 of 96 individuals who received placebo (92%) were successfully infected, whereas 69 of 81 subjects that were administered tremacamra intranasally were successfully infected (85%) [68]. Although this difference was not statistically significant ($P = 0.190$), symptoms and nasal mucous quantity were significantly reduced ($P < 0.001$). Whether this effect of tremacamra would be sufficient to influence the course of asthma that was induced by rhinovirus infection remains to be investigated. If one of these medications can be effective and sufficiently benign to use prophylactically, at least throughout the viral respiratory disease season, the frequency of asthma exacerbations could be greatly reduced.

Concluding comments

Asthma frequently begins in early childhood with a viral respiratory infection that induces lower respiratory illness. In infancy, the most common viral respiratory infection responsible for causing lower respiratory illness is RSV, which, in genetically susceptible individuals, results in repeated episodes of lower respiratory illness in early childhood that are consistent with a diagnosis of asthma. Although these recurrent exacerbations of asthma from RSV and other common cold viruses is self-limited for many of these children, some, particularly those who develop atopic type of allergic responses to inhalant allergens, go on to have persistent asthma. Viral respiratory infections continue to be the major causes of acute exacerbations of asthma in children and adults, and are not

prevented with any of the currently available maintenance medications that are used for chronic asthma, including the most effective agents – inhaled corticosteroids. Current effective treatment for viral respiratory infection-induced asthma requires early intervention with systemic corticosteroids. Medication that would prevent or substantially ameliorate RSV and rhinovirus infection would be highly desirable. There is continued research to develop a safe and effective RSV vaccine, and several antiviral agents that are effective against RSV are at various stages of development and investigation. Strategies for preventing and treating rhinovirus have focused on the major respiratory epithelial receptor for this virus, ICAM-1. A genetically modified soluble ICAM-1 has shown some clinical effect on experimental rhinovirus infection in humans, and a monoclonal antibody to ICAM-1 with a greater avidity than previous attempts is judged to be worth further preclinical and clinical testing. Successful development of effective and safe measures to prevent and treat infection with these common cold viruses would have a major impact on decreasing acute exacerbations of asthma that result in urgent medical care and hospitalizations from this common disease.

References

1 Lemanske, R.F., Jr. (2003) Viruses and asthma: inception, exacerbations, and possible prevention. *J. Pediatr.* 142, S3–S8
2 Glezen, W.P. *et al.* (1986) Risk of primary infection and reinfection with respiratory syncytial virus. *Am. J. Dis. Child.* 140, 543–546
3 Shay, D.K. *et al.* (1999) Bronchiolitis-associated hospitalizations among US children, 1980–1996. *J. Am. Med. Assoc.* 282, 1440–1446
4 Sims, D.G. *et al.* (1978) Study of 8-year-old children with a history of respiratory syncytial virus bronchiolitis in infancy. *Br. Med. J.* 1, 11–14
5 Gurwitz, D. *et al.* (1981) Increased incidence of bronchial reactivity in children with a history of bronchiolitis. *J. Pediatr.* 98, 551–555
6 Welliver, R.C. *et al.* (1986) Predictive value of respiratory syncytial virus-specific IgE responses for recurrent wheezing following bronchiolitis. *J. Pediatr.* 109, 776–780
7 Sigurs, N. *et al.* (2000) Respiratory syncytial virus bronchiolitis in infancy is an important risk factor for asthma and allergy at age 7. *Am. J. Respir. Crit. Care Med.* 161, 1501–1507
8 Weinberger, M. (2003) Clinical patterns and natural history of asthma. *J. Pediatr.* 142 (Suppl. 2), S15–S20
9 McIntosh, K. *et al.* (1973) The association of viral and bacterial respiratory infections with exacerbations of wheezing in young asthmatic children. *J. Pediatr.* 82, 578–590
10 Minor, T.E. *et al.* (1974) Viruses as precipitants of asthmatic attacks in children. *J. Am. Med. Assoc.* 227, 292–298
11 Nicholson, K.G. *et al.* (1993) Respiratory viruses and exacerbations of asthma in adults. *Br. Med. J.* 307, 982–986
12 Johnston, S.L. *et al.* (1995) Community study of role of viral infections in exacerbations of asthma in 9–11 year old children. *Br Med. J.* 310, 1225–1229
13 Rakes, G.P. *et al.* (1999) Rhinovirus and respiratory syncytial virus in wheezing children requiring emergency care: IgE and eosinophil analyses. *Am. J. Respir. Crit. Care Med.* 159, 785–790
14 Dales, R.E. *et al.* (1996) Respiratory infections and the autumn increase in asthma morbidity. *Eur. Respir. J.* 9, 72–77
15 Rosenstein, N. *et al.* (1998) The common cold – principles of judicious use of antimicrobial agents. *Pediatrics* 101, 181–184
16 Akinbami, L.J. and Schoendorf, K.C. (2002) Trends in childhood asthma: prevalence, health care utilization, and mortality. *Pediatrics* 110, 315–322
17 Chew, F.T. and Lee, B.W. (1998) Utilization of healthcare resources for asthma in Singapore: demographic features and trends. *Asian Pac. J. Allergy Immunol.* 16, 57–68
18 Korhonen, K. *et al.* (2002) Hospitalization trends for paediatric asthma in eastern Finland: a 10 year survey. *Eur. Respir. J.* 19, 1035–1039
19 Engelsvold, D.H. and Oymar, K. (2003) Hospital admissions for childhood asthma in Rogaland, Norway from 1984 to 2000. *Acta Paediatr.* 92, 610–616
20 Johnston, S.L. *et al.* (1996) The relationship between upper respiratory infections and hospital admissions for asthma: a time-trend analysis. *Am. J. Respir. Crit. Care Med.* 154, 654–660
21 Jartti, T. *et al.* (2002) Metapneumovirus and acute wheezing in children. *Lancet* 360, 1393–1394
22 Peiris, J.S. *et al.* (2003) Children with respiratory disease associated with metapneumovirus in Hong Kong. *Emerg. Infect. Dis.* 9, 628–633
23 Rawlinson, W.D. *et al.* (2003) Asthma exacerbations in children associated with rhinovirus but not human metapneumovirus infection. *J. Infect. Dis.* 187, 1314–1318
24 Williams, J.V. *et al.* (2004) Human metapneumovirus and lower respiratory tract disease in otherwise healthy infants and children. *N. Engl. J. Med.* 350, 443–450
25 Martin, R.J. *et al.* (2001) A link between chronic asthma and chronic infection. *J. Allergy Clin. Immunol.* 107, 595–601
26 Jones, K. and Gruffydd-Jones, K. (1996) Management of acute asthma attacks associated with respiratory tract infection: a postal survey of general practitioners in the UK. *Respir. Med.* 90, 419–425
27 Henderson, M. and Rubin, E. (2001) Misuse of antimicrobials in children with asthma and bronchiolitis: a review. *Pediatr. Infect. Dis. J.* 20, 214–215
28 Shapiro, G.G. *et al.* (1974) Double-blind study of the effectiveness of a broad-spectrum antibiotic in status asthmaticus. *Pediatrics* 53, 867–872
29 Graham, V.A. *et al.* (1982) Routine antibiotics in hospital management of acute asthma. *Lancet* 1, 418–420
30 Sachs, A.P. *et al.* (1995) Changes in symptoms, peak expiratory flow, and sputum flora during treatment with antibiotics of exacerbations in patents with chronic obstructive pulmonary disease in general practice. *Thorax* 50, 758–763
31 Kraft, M. *et al.* (2002) *Mycoplasma pneumoniae* and *Chlamydia pneumoniae* in asthma: effect of clarithromycin. *Chest* 121, 1782–1788
32 Beuther, D.A. and Martin, R.J. (2004) Antibiotics in asthma. *Curr. Allergy Asthma Rep.* 4, 132–138
33 Storr, J. *et al.* (1987) Effect of a single oral dose of prednisolone in acute childhood asthma. *Lancet* 1, 879–882
34 Tal, A. *et al.* (1990) Methylprednisolone therapy for acute asthma in infants and toddlers: a controlled clinical trial. *Pediatrics* 86, 350–356
35 Scarfone, R.J. *et al.* (1993) Controlled trial of oral prednisone in the emergency department treatment of children with acute asthma. *Pediatrics* 92, 513–518
36 Schuh, S. *et al.* (2002) Efficacy of oral dexamethasone in outpatients with acute bronchiolitis. *J. Pediatr.* 140, 27–32
37 Weinberger, M. (2003) Corticosteroids for first time young wheezers: current status of the controversy. *J. Pediatr.* 143, 700–702
38 Harris, J.B. *et al.* (1987) Early intervention with short courses of prednisone to prevent progression of asthma in ambulatory patients incompletely responsive to bronchodilators. *J. Pediatr.* 110, 627–644
39 Brunette, M.G. *et al.* (1988) Childhood asthma: prevention of attacks with short-term corticosteroid treatment of upper respiratory tract infection. *Pediatrics* 81, 624–629
40 Weinberger, M. (1988) Commentary – corticosteroids for exacerbations of asthma: current status of the controversy. *Pediatrics* 81, 726–729

41 Weinberger, M. (2000) Corticosteroids for exacerbations of asthma: problems and solutions. *J. Pediatr.* 136, 276–278
42 Weinberger, M. (2003) Treatment strategies for viral respiratory infection-induced asthma. *J. Pediatr.* 142 (Suppl. 2), S34–S39
43 Ducharme, F.M. *et al.* (2003) Safety profile of frequent short courses of oral glucocorticoids in acute pediatric asthma: impact on bone metabolism, bone density, and adrenal function. *Pediatrics* 111, 376–383
44 Doull, I.J. (2003) Limitations of maintenance therapy for viral respiratory infection-induced asthma. *J. Pediatr.* 142, S21–S25
45 Wilson, N. *et al.* (1995) Effect of continuous treatment with topical corticosteroid on episodic viral wheeze in preschool children. *Arch. Dis. Child.* 72, 317–320
46 Stick, S.M. *et al.* (1995) The effects of inhaled beclomethasone dipropionate on lung function and histamine responsiveness in recurrently wheezy infants. *Arch. Dis. Child.* 73, 327–332
47 Doull, I.J. *et al.* (1997) Effect of inhaled corticosteroids on episodes of wheezing associated with viral infection in school age children: randomized double-blind placebo-controlled trial. *Br. Med. J.* 315, 858–862
48 McKean, M. and Ducharme, F. (2004) Inhaled steroids for episodic viral wheeze of childhood (Cochrane Review). In *The Cochrane Library,* Issue 3, John Wiley & Sons
49 Grunberg, K. *et al.* (2000) Experimental rhinovirus 16 infection increase intracellular adhesion molecule-1 expression in bronchial epithelium of asthmatics regardless of inhaled steroid treatment. *Clin. Exp. Allergy* 30, 1015–1023
50 Rodriguez, W. *et al.* (1997) Respiratory syncytial virus immune globulin intravenous therapy for RSV lower respiratory tract infection in infants and young children at high risk for severe RSV infections. *Pediatrics* 99, 454–461
51 Rodriguez, W. *et al.* (1997) Respiratory syncytial virus immune globulin treatment of RSV lower respiratory tract infection in previously healthy children. *Pediatrics* 100, 937–946
52 The Impact-RSV Study Group (1998) Palivizumab, a humanized respiratory syncytial virus monoclonal antibody reduces hospitalization from respiratory syncytial virus infection in high-risk infants. *Pediatrics* 102, 531–537
53 Kapikian, A.Z. *et al.* (1969) An epidemiologic study of altered clinical reactivity to respiratory syncytial (RS) virus infection in children previously vaccinated with an inactivated RS virus vaccine. *Am. J. Epidemiol.* 89, 405–421
54 Kim, H.W. *et al.* (1969) Respiratory syncytial virus disease in infants despite prior administration of antigenic inactivated vaccine. *Am. J. Epidemiol.* 89, 422–434
55 Prince, G.A. *et al.* (1986) Enhancement of respiratory syncytial virus pulmonary pathology in cotton rats by prior intramuscular inoculation of formalin-inactivated virus. *J. Virol.* 57, 721–728
56 Connors, M. *et al.* (1994) Enhanced pulmonary histopathology induced by respiratory syncytial virus (RSV) challenge of formalin-inactivated RSV-immunized BALB/c mice is abrogated by depletion of interleukin-4 (IL-4) and IL-10. *J. Virol.* 68, 5321–5325
57 Openshaw, P.J. *et al.* (2001) Immunopathogenesis of vaccine-enhanced RSV disease. *Vaccine* 20 (Suppl. 1), S27–S31
58 Polack, F.P. and Karron, R.A. (2004) The future of respiratory syncytial virus vaccine development. *Pediatr. Infect. Dis. J.* 23 (Suppl. 1), S65–S73
59 Edell, D. *et al.* (2002) Early ribavirin treatment of bronchiolitis: effect on long-term respiratory morbidity. *Chest* 122, 935–939
60 Guerguerian, A.M. *et al.* (1999) Ribavirin in ventilated respiratory syncytial virus bronchiolitis. A randomized, placebo-controlled trial. *Am. J. Respir. Crit. Care Med.* 160, 829–834
61 Maggon, K. and Sailen, B. (2004) New drugs and treatment for respiratory syncytial virus. *Rev. Med. Virol.* 14, 149–168
62 Suzuki, T. *et al.* (2002) Erythromycin inhibits rhinovirus infection in cultured human tracheal epithelial cells. *Am. J. Respir. Crit. Care Med.* 165, 1113–1118
63 Greve, J.M. *et al.* (1989) The major human rhinovirus receptor is ICAM-1. *Cell* 56, 839–847
64 Staunton, D.E. *et al.* (1989) A cell adhesion molecule, ICAM-1 is the major surface receptor for rhinoviruses. *Cell* 56, 849–853
65 Hayden, F.G. *et al.* (1988) Modification of experimental rhinovirus colds by receptor blockade. *Antiviral Res.* 9, 233–247
66 Charles, C.H. *et al.* (2003) Prevention of human rhinovirus infection by multivalent fab molecules directed against ICAM-1. *Antimicrob. Agents Chemother.* 47, 1503–1508
67 Fang, F. and Yu, M. (2004) Viral receptor blockage by multivalent recombinant antibody fusion proteins: inhibiting human rhinovirus (HRV) infection with CFY196. *J. Antimicrob. Chemother.* 53, 23–25
68 Turner, R.B. *et al.* (1999) Efficacy of tremacamra, a soluble intercellular adhesion molecule 1, for experimental rhinovirus infection: a randomized clinical trial. *J. Am. Med. Assoc.* 281, 1797–1804