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REVIEW

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Therapy for respiratory tract infections caused by respiratory syncytial virus

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Abstract Respiratory syncytial virus (RSV) is the most common viral cause of lower respiratory tract infection (LRTI) in infancy and young children. No effective treatment for RSV lower respiratory tract infection (RSV-LRTI) exists. Ribavirin initially proved to be an effective anti-viral drug for RSV-LTRI. However, subsequently performed trials could not reproduce these positive results and, based on the current available evidence, there is no place for ribavirin in the routine treatment of RSV-LTRI. The use of nebulised bronchodilator therapy in RSV-LTRI has been subject of many trials, with conflicting results. Although the individual patient may have some short-term benefit from nebulised bronchodilators, there does not seem to be a sufficient scientific basis for the standard use of bronchodilator therapy in infants and children with RSV-LTRI. There is increasing evidence that RSV-LTRI is an immune-mediated disease and therefore corticosteroids may be an effective treatment. The results from efficacy trials have demonstrated that corticosteroids are not effective for patients with mild RSV infection. In contrast there are indications that it may be beneficial in patients with more severe RSV-LTRI. It has been demonstrated that in children with RSV infection the vitamin A concentration is inversely related to disease severity. The use of vitamin A in the treatment of patients with RSV-LTRI, however, proved not to be effective. Immunoprophylaxis with hyperimmune immunoglobulins and monoclonal antibody against the viral F-protein have been shown to be effective in the prevention of RSV-LRTI. From the results of the therapeutic efficacy trials, however, it can be discerned that immunoglobulins have no place in the treatment of RSV-LRTI.

Conclusion Although respiratory syncytial virus infections each year have a considerable socioeconomic impact, attempts to find an effective therapy have so far been quite unsuccessful. Anti-viral therapy with ribavirin has not been proven to be effective. Symptomatic therapy with bronchodilators may give only short-term relief of symptoms in some individual patients, but has no effect on hospitalisation rates, or duration of hospitalisation. The beneficial effect of corticosteroids in patients with mild respiratory syncytial virus infection is very disappointing, however, there are indications that there might be an effect in patients with more severe infection. So far no beneficial therapeutic effect has been demonstrated with immune globulins.

Key words Respiratory syncytial virus · Respiratory tract infection · Treatment · Review

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Abbreviations *FI-RSV* formalin inactivated respiratory syncytial virus · *IVIG* standard intravenous immune globulin · *LRTI* lower respiratory tract infection · *RSV* respiratory syncytial virus · *RSVIG* hyperimmune RSV globulins · *RSV-LRTI* respiratory syncytial virus lower respiratory tract infection

Introduction

Respiratory syncytial virus (RSV) is the most common viral cause of lower respiratory tract infection (LRTI) in infancy and young children [18]. RSV infection usually starts in the upper respiratory tract. In 25%–40% of cases the lower respiratory tract is also involved [24]. In the general population only about 1% of children infected with RSV need hospitalisation due to severe illness [24]. In the Netherlands between 800 and 2500 children are admitted to hospital annually for RSV lower respiratory tract infection (RSV-LRTI). In industrialised countries the mortality rate for children admitted to hospital for RSV-LRTI has been reported to be between 1%–3% although this varies greatly with the population [24]. Patients with pre-existent pulmonary disease such as bronchopulmonary dysplasia and cystic fibrosis or with congenital heart disease, as well as ex-premature and very young children form high risk groups for severe RSV infection. Whereas LRTI or LRTI with RSV is typically a disease of immunocompetent infants and young children, immunocompromised patients may develop severe RSV pneumonia [27, 51].

No effective treatment for RSV-LRTI exists. Antiviral, bronchodilator and anti-inflammatory therapy for RSV-LTRI have been subject of a large number of clinical trials. These trials have shown conflicting results, which contributes to an inconsistent approach to patients with RSV infection world-wide [4, 35].

Therapy

General considerations

In the development of therapeutic strategies for RSV bronchiolitis the role of the immune response should be taken in account. An increasing body of evidence has demonstrated that besides a direct cytotoxic effect of RSV, parts of the immune response against RSV may contribute to the pathogenesis. The first indications for this role of the immune response came from the experiences with formalin-inactivated virus (FI-RSV) that was used as a vaccine in the 1960s. After vaccination with FI-RSV, children developed severe LRTI when subsequently infected with RSV the next season. In the lungs of patients dying of a natural infection after vaccination, infiltrates of mononuclear cells and eosinophils were found. The mechanism responsible for this vaccine-associated enhanced disease is still not completely understood. There are indications that formalin changes viral epitopes responsible for the generation of neutralising antibodies [13]. In addition, from animal studies it became clear that a natural infection with RSV elaborates a Th-1-like response whereas the FI-RSV vaccine leads to a Th-2-like response giving rise to increased airway inflammation [13].

Subsequent experimental studies have shown that also during natural infection the immune response may contribute to enhanced disease. In an experimental model Cannon et al [6] infected immunodeficient mice with RSV. They demonstrated that only those mice that received RSV-specific cytotoxic T-cells concomitant with the virus died. Graham et al. [20] demonstrated less morbidity in CD-4 and CD-8 T-cell deficient mice after infected with RSV when compared with immune-competent mice. In contrast to these clear immunopathogenetic effects of the cellular immune response, a pre-existing humoral response is mainly associated with protection against RSV infection. Several studies have demonstrated that the risk of LRTI is inversely related to the titre of neutralising antibodies [28]. However, there are also indications that besides this protective effect, parts of the humoral immune response may be associated with the pathogenesis of RSV bronchiolitis [34]. Finally, also in the similarities between asthma and RSV bronchiolitis arguments for immunopathogenesis can be found. Asthma and RSV bronchiolitis do have many features in common. Both in asthma as in RSV-LRTI eosinophils play an important role in the inflammation of the airways [17].

In summary it can be stated that the humoral response is associated with protection against RSV infection, and that the cellular immune response terminates RSV disease, but in the meanwhile contributes to enhanced disease severity. The fact that RSV disease is a partially immune-mediated disease may on the one hand explain why results with antiviral therapy are disappointing, on the other hand it may give opportunities for immune modulating therapy, for example with corticosteroids or immune globulins.

Antiviral therapy

Ribavirin is a synthetic nucleoside analogue and is the only antiviral drug against RSV that is available. For RSV infection it is only registered in nebulised form, given as a small particle aerosol. The first clinical intervention trials that evaluated the efficacy of nebulised ribavirin were conducted in the early 1980s in patients with RSV-LRTI who did not receive mechanical ventilation [3, 23, 25, 26, 32, 64]. Most of these trials showed a positive effect of nebulised ribavirin when compared with placebo treatment. However, randomisation and

blinding procedures were not properly conducted [3], or only improvement of non-validated illness severity scores and/or oxygenation changes were used as primary endpoints [23, 25, 26, 64]. In none of these studies duration of hospitalisation was used as an endpoint. In addition, none of these trials corrected for concomitant treatment during hospitalisation for example with bronchodilator therapy or steroids. In an attempt to include these studies in a meta-analysis the way each study reported their data prevented aggregation and no conclusion could be drawn [53].

Smith et al. [61] were the first to study ribavirin in patients with severe RSV-LRTI who received mechanical ventilation. In a double-blind placebo-controlled study they demonstrated that in patients treated with nebulised ribavirin the mean duration of mechanical ventilation, the use of supplemental oxygen as well as the length of hospital stay were significantly shorter when compared with the placebo-treated patients. This study was criticised because water was used as a placebo, which is a possible irritant for the airways when compared with standard mechanical ventilation with humidified air [48]. A further double-blind placebo-controlled study in mechanically ventilated patients with RSV-LRTI in whom isotonic saline solution was used as placebo could not demonstrate a positive effect of ribavirin on the same variables [45]. Moreover, Moler et al [49] showed in a controlled trial that nebulised ribavirin may even lead to prolongation of mechanical ventilation in infants with RSV-associated respiratory failure. In addition, Law et al [39] demonstrated that the use of ribavirin was associated with a prolonged duration of hospitalisation in patients with RSV-LRTI. Based on the results of the latter three studies in addition to a historical cohort study that failed to demonstrate a positive effect of ribavirin [69], the American Academy of Pediatrics made a reassessment of its use. The Academy changed their recommendation from 'should be used' to 'may be considered' in high risk children for serious RSV disease [2].

In conclusion, ribavirin has no proven benefit as an anti-viral treatment in RSV infection and based on the current available evidence there is no place for its routine use in either ventilated or non-ventilated patients with RSV-LRTI.

Bronchodilator therapy

As in asthma, airway obstruction secondary to inflammation and constriction of the smaller airways plays an important role in the pathophysiology of bronchiolitis. Therefore, it is not surprising that bronchodilator therapy has been subject of many trials in patients with bronchiolitis. However, these trials have shown conflicting results. In part, this may be due to different inclusion criteria, since not all patients in these trials had proven RSV infection and many asthma patients may have been included. In addition these trials used different treatment strategies as well as different endpoints. Most of the studies have evaluated the efficacy of β-2-agonists in bronchiolitis, both in inpatient as in outpatient settings.

β-2-Agonists

The results of randomised controlled trials evaluating the effects of nebulised β-2-agonists in bronchiolitis in hospitalised patients are shown in Table 1. In one (unblinded) study, a positive effect on a severity score and length of hospital stay was found [44]. All other studies failed to demonstrate a positive effect of nebulised β-2-agonists on severity scores or length of hospital stay.

Table 1 Randomised controlled trials evaluating the efficacy of nebulised β-2-agonists in hospitalised patients with bronchiolitis. (*AP* aminophylline, *CO* cross over, *DB* double blind, *IB* ipratropium bromide, *PC* placebo-controlled, *R* randomised, *S* systemic corticosteroids)

Study	*N*	Design	RSV⊕/tested (%)	Treatment	Variables	Results
[31]	21	R-DB-PC-CO	21/21 (100)	Albuterol	Oxygen saturation	Negative
[44]	79	R-PC	Not stated	Fenoterol	Standardised severity score	Positive
				Fenoterol + IB	Length of hospital stay	Positive
				Oral fenoterol + S		
				Oral fenoterol + S + AP		
[68]	62	R-DB-PC	16/60 (27)	Albuterol a/o IB	Oxygen saturation	Negative
					Standardised severity score	No difference
					Length of hospital stay	No difference
[11]	52	R-DB-PC	42/52 (81)	Albuterol	Oxygen saturation	No difference
					Standardised severity score	No difference
					Length of hospital stay	No difference
[42]	49	R-DB-PC	20/32 (41)	Albuterol	Oxygen saturation	Negative
					Standardised severity score	No difference
[19]	120	R-DB-PC	51/120 (42)	Albuterol or IB	Standardised severity score	No difference
					Number of nebulisations	No difference
					Length of hospital stay	No difference
[7]	89	R-DB-PC	52/74 (70)	Albuterol a/o IB	Standardised severity score	No difference
					Length of hospital stay	No difference

Several studies even showed a negative effect on oxygen saturation [31, 42, 68]. It is important to mention that proportions of patients with laboratory proven RSV infection varied strongly in these studies: from 27%–100%. As shown in Table 2, several studies have evaluated the effect of β-2-agonists in an outpatient setting. Some of them found a positive effect in terms of severity scores, while others did not. In addition the rate of hospitalisation was no different in any of the studies. Also in these studies there was a great variation in the proportion of RSV-infected patients, from 34%–62%.

Other bronchodilator therapy

Several other bronchodilator drugs have been subject of randomised placebo controlled trials. In hospitalised patients ipratropium bromide proved to be not effective, either alone or in combination with β-2-agonists, in terms of oxygen saturation, severity score, number of nebulisations, or length of hospital stay [7, 19, 30, 41, 44, 68].

The effect of epinephrine on bronchiolitis has also been evaluated in randomised controlled trials. The first trial was performed in 1983 by Lowell et al [43]. They found that subcutaneous epinephrine had a positive effect on a severity score in an outpatient setting. Another trial was performed in an inpatient setting and evaluated the effect of nebulised epinephrine [38]. The results of this study also demonstrated a positive effect of epinephrine when compared with placebo on a severity score. However, the subjects in both these studies were not proven RSV-infected children, a severity score was the only endpoint and only a very short-term effect (30 and 60 min respectively) was measured. Two studies compared the effect of nebulised epinephrine with nebulised salbutamol [47, 58] In one study epinephrine proved to be superior to salbutamol in terms of a severity score and lung function when measured after 15–30 min [58]. The other study showed a better oxygen saturation and significantly less hospitalisations in the epinephrine group [47]. These two studies were not placebo-controlled. The rationale for the use of epinephrine for bronchiolitis lies in the combination of a α- and β-effects. Besides bronchoconstriction, intraluminar oedema plays an important role due to the infection. The α-effect leads to reduction of capillary and post-capillary leakage which in turn may result in less oedema. The effect of epinephrine should be further evaluated in larger placebo controlled trials.

Meta-analysis

Three [31, 44, 68] of the seven inpatient studies shown in Table 1 were enrolled in a recently performed meta-analysis of randomised controlled trials evaluating the efficacy of nebulised β-2-agonists [14]. No firm conclusion could be drawn, because the variability of the design and outcome of these three studies prevented aggregation of the data. The same meta-analysis enrolled five [15, 16, 36, 59, 60] of the six outpatient randomised controlled trials shown in Table 2. The pooled data contained 129 patients in the β-2-agonist group versus 122 in the placebo group. No beneficial effect of β-2-agonists could be demonstrated on hospitalisation rate, while there was little impact on physiological status (severity scores) when compared with placebo treated patients [14].

Kellner et al. [33] published another meta-analysis of 20 both in- and outpatient randomised controlled trials that evaluated bronchodilator therapy in bronchiolitis. The authors found that bronchodilator therapy was beneficial in terms of clinical severity score. We, however, question the clinical relevance of this finding, moreover since no difference could be demonstrated on more long-term endpoints such as rate of hospitalisation or length of hospital stay. The results of this meta-analysis may be biased by inclusion of many non-bronchiolitis patients. In addition, the interpretation of

Table 2 Randomised controlled trials evaluating the effect nebulised β-2-agonists in an outpatient setting. (*CO* cross over, *DB* double blind, *PC* placebo-controlled, *R* randomised)

Study	*N*	Design	RSV⊕/tested (%)	Treatment	Variables	Results
[1]	74	R-DB-PC-CO	21/62 (34)	Metaproterenol	Standardised severity score	Positive
[59]	40	R-DB-PC	21/34 (62)	Albuterol	Oxygen saturation	Positive
					Standardised severity score	Positive
					Hospitalisation rate	No difference
[36]	83	R-DB-PC	48/83 (58)	Albuterol	Oxygen saturation	No difference
					Standardised severity score	Positive
					Hospitalisation rate	No difference
[16]	88	R-DB-PC	36/75 (48)	Albuterol	Oxygen saturation	No difference
					Standardised severity score	No difference
					Hospitalisation rate	No difference
[15]	128	R-DB-PC	51/118 (43)	Albuterol	Oxygen saturation	No difference
					Standardised severity score	No difference
[60]	25	R-DB-PC	Not stated	Albuterol	Oxygen saturation	Negative/No difference
					Standardised severity score	Positive
					Hospitalisation rate	No difference

the results may be difficult since no differentiation was made between different bronchodilators.

The individual patient may have some short-term benefit from nebulised bronchodilators. However there does not seem to be a sufficient scientific basis for the standard use of bronchodilator therapy in children and infants with RSV bronchiolitis. More placebo-controlled trials should be done to evaluate the effect of epinephrine in RSV bronchiolitis.

Corticosteroids

As discussed above, there is an increasing body of both experimental and clinical evidence that the immune response in RSV bronchiolitis may be disease-enhancing. Because RSV bronchiolitis is an immune-mediated disease, immune-modulating drugs like corticosteroids may be effective. Already since the early 1960s this has been subject of several clinical trials with conflicting results as is shown in Table 3. The first trial was done by Oski et al. in 1961 [52]. They found a positive effect of dexamethasone on a severity score, length of oxygen therapy and hospital stay. Some subsequently performed studies could not reproduce their results [40, 62, 63] while others also found positive effects of corticosteroids in patients with bronchiolitis [9, 65]. Due to different treatment protocols and variable study populations with unknown proportions of RSV-infected children, these trials are not comparable and may be difficult to interpret.

As is shown in Table 4, more recently five randomised controlled trials studied the effect of corticosteroids in the treatment of RSV-proven bronchiolitis [8, 10, 37, 57, 67]. In four of these trials no beneficial effect of corticosteroids could be demonstrated in terms of severity score, oxygen saturation and oxygen use, lung function as well as length of hospital stay [8, 10, 37, 57]. However, in all these four studies, patients with severe bronchiolitis and patients who needed mechanical ventilation were excluded. In a randomised placebo-controlled trial, our group could indeed not demonstrate a beneficial effect of oral prednisolone in patients with mild RSV bronchiolitis. However, in patients with severe infection we found that prednisolone was effective. In non-ventilated patients we found a faster clinical recovery in the prednisolone group when compared with the placebo group. In addition in ventilated patients we found that prednisolone led to a significant shorter duration of hospitalisation of 6 days [67]. These results formed the base for a new multicentre trial that is currently underway. In this trial the effect of corticosteroids is evaluated in patients who need mechanical ventilation because of respiratory insufficiency due to severe RSV bronchiolitis.

Table 3 Clinical trials evaluating the effect of corticosteroids in bronchiolitis. (*DB* double blind, *PC* placebo-controlled, *R* randomised)

Study	*N*	Design	RSV⊕/tested (%)	Treatment (days)	Variables	Results
[52]	20	R-PC	Unknown	Dexamethasone (2)	Standardised severity score	Positive
					Length of oxygen therapy	Positive
					Length of hospital stay	Positive
[63]	59	DB-PC	14/26 (54)	Dexamethasone (14)	Disease severity	No difference
[9]	44	R-DB-PC	Unknown	Methylprednisolone (2)	Standardised severity score	No difference
					Length of hospital stay	Positive
[40]	297	R-DB-PC	Unknown	Betamethasone (3)	Disease severity	No difference
[65]	32	R-DB-PC	Unknown	Dexamethasone (3)	Standardised severity score	Positive
[62]	50	R-DB-PC	Unknown	Hydrocortisone,	Standardised severity score	No difference
				Prednisolone (8)	Lung function	No difference
					Length of hospital stay	No difference

Table 4 Randomised placebo-controlled trials evaluating the effect in RSV-proven bronchiolitis. (*DB* double blind, *PC* placebo-controlled, *R* randomised)

Study	*N*	Design	RSV⊕/tested (%)	Treatment (days)	Variables	Results
[8]	95	R-DB-PC	78/93 (84)	Prednisolone (7)	Disease severity	No difference
[57]	118	R-DB-PC	79/118 (67)	Dexamethasone (3)	Length of oxygen therapy	No difference
					Standardised severity score	No difference
[37]	67	R-DB-PC	58/67 (87)	Dexamethasone (3)	Standardised severity score	No difference
					Oxygen saturation	No difference
					Length of hospital stay	No difference
[10]	29	R-DB-PC	29/29 (100)	Dexamethasone (3)	Standardised severity score	No difference
					Oxygen saturation	No difference
					Lung function	No difference
					Length of hospital stay	No difference
[67]	54	R-DB-PC	54/54 (100)	Prednisolone (7)	Standardised severity score	Positive
					Length of ventilation	Positive
					Length of hospitalisation	Positive

Vitamin A

It has been demonstrated that children with RSV infection have depressed vitamin A concentrations and that vitamin A concentration is inversely related to disease severity [50]. Subsequently, in two randomised controlled efficacy trials, vitamin A was compared with placebo in children hospitalised for RSV infection [5, 12]. The results of these trials showed that children with RSV infection do not benefit from high dose vitamin A supplementation. In one trial children older than 1 year who received vitamin A even had longer hospital stay than those receiving placebo [5]. In conclusion the use of vitamin A in RSV bronchiolitis is not supported by the current evidence.

Immunoglobulins

Because attempts to develop a safe vaccine against RSV has had only limited success to date, much effort has been focused on the role of immunoglobulins in the prevention of RSV infection. Encouraged by results from animal studies, several investigators also have evaluated the therapeutic effect of immunoglobulins in patients with RSV bronchiolitis. Standard intravenous immune globulin (IVIG) proved neither to be protective [46] nor to have a therapeutic effect [29]. It was suggested that with standard IVIG used in these studies insufficient neutralising antibody titres were achieved. This was also the case in several other lots of standard IVIG tested [28]. In the search for alternatives, hyperimmune globulins with higher neutralising antibody titre against RSV (RSVIG) were developed. It proved that RSVIG indeed could provide better neutralising antibody titres [22, 28]. In a randomised prevention trial, monthly administered high dose intravenous RSVIG proved to be beneficial in terms of rate of hospitalisation, duration of hospitalisation and duration on the intensive care unit in children at high risk for severe RSV infection [21]. In contrast with this positive effect in preventing RSV-LRTI with RSVIG, the results of two treatment intervention trials with RSVIG were disappointing. Compared with placebo, RSVIG was not effective in healthy children with RSV infection in terms of length of hospital stay, stay on the intensive care unit, mechanical ventilation or oxygen therapy [55]. Also in children at high risk for severe RSV infection, treatment with RSVIG proved not to be beneficial [56]. Rimensberger et al. [54] evaluated the effect of aerosolised immune globulins in patients hospitalised for RSV bronchiolitis in a double-blind controlled study design. Neither with this form of administration of immune globulin could a beneficial clinical or microbiological effect be demonstrated. From the studies with RSVIG it became clear that passive immunisation is effective as long as enough neutralising antibody titre is achieved. However, RSVIG has several disadvantages. It requires monthly intravenous infusions with a high fluid load and is very costly. Therefore further research has been done to develop an alternative preparation. Palivizumab is a humanised monoclonal antibody against the F-protein of RSV. It can be given intramuscularly and proved to reduce hospital admissions for RSV infectious with 55% when given as monthly injections [66]. No therapeutic data on Palivizumab are available to date.

In conclusion, immunoprophylaxis seems to be protective, as long as sufficient titres of neutralising antibodies against RSV are provided. In contrast, from the therapeutic efficacy trials conducted so far, it has become clear that there is no place for immune globulin in the routine treatment of RSV bronchiolitis.

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